CHOLERA

AND ITS TREATMENT

LEONARD ROGERS

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"I MUST say, however, that it appears to me the profession in India requires a little gentle stimulation in this direction; it would seem as if we had almost abandoned ourselves to despair in this matter of the treatment of cholera; doubtless the task is beset with difficulties, but this should not depress but rather stimulate research, where the good of our fellows and the honour of our profession are so deeply concerned. The solution of the question, I repeat, is one which pre-eminently devolves upon men living in the endemic area of cholera, and it is to us, therefore, that the profession in Europe naturally turn for information on these matters."—C. MACNAMARA.

PREFACE

NEARLY twenty years have elapsed since the appearance of Wall's excellent work on cholera, so perhaps a fresh attempt in this direction may be excusable. The appearance of most of the former Anglo-Indian works on cholera have been closely related to the epidemic prevalence of the disease in Europe. Although the present little book is no exception to this rule, the coincidence is an accidental one, for it was planned and commenced nearly three years ago, with a view to combining the accumulated knowledge and experience of the last century with the system of treatment based on the writer's researches on the blood and circulatory changes in cholera which have recently resulted in a very great reduction of the death rate among cases treated in Calcutta and elsewhere in India.

The author has carefully studied former works by writers with Indian experience and is especially indebted to C. Macnamara's classical *History of Cholera* for nearly all the information in the first section. For convenience of reference the historical

data have been embodied in a series of maps illustrating the spread of the principal European epidemics. The only other feature worthy of note is that nearly one-third of the work is devoted to a description of the practical details of the treatment of cholera, as in the opinion of the writer there is no important specific disease in which a larger proportion of lives can be saved by simple measures carried out at the right time. Should this work enable others to obtain similar results to those of the last three years in Calcutta, the writer will have no need to apologize for again submitting to the profession a work on an important tropical disease.

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LIST OF THE MORE IMPORTANT WORKS ON CHOLERA

1. *Report on the Epidemic Cholera Morbus; as it visited the Territories subject to the Presidency of Bengal in the years* 1817, 1818, *and* 1819. Drawn up by order of the Government, under the superintendence of the Medical Board. By James Jameson, Assistant Surgeon and Secretary to the Board. Calcutta, 1820.

2. *An Essay on the Epidemic Cholera of India by Reginald Orton.* Madras, 1820.

3. *Sketches of the most prevalent diseases of India: comprising a treatise on the Epidemic Cholera of the East; statistical and topographical reports on the diseases in the different divisions of the Army under the Madras Presidency, &c.* By James Annesley, Esq. London, 1825.

4. *Notes on the Epidemic Cholera.* By R. Hartley Kennedy, M.D., late Physician General, and President of the Medical Board. Bombay, 1826. Reprinted 1846.

5. *A Treatise on the Epidemic Cholera; as it prevailed in India, together with the reports of the medical officers made to the medical boards of the Presidencies of Bengal, Madras, and Bombay, for the purpose of ascertaining a successful mode of treating that destructive disease, and a critical examination of all the works which have appeared on the subject.* By Frederick Corbyn. Calcutta, 1832.

6. *A Practical Account of the Epidemic Cholera, and of the treatment requisite in the various modifications of that disease.* By William Twining, of the Royal College of Surgeons, London; First Assistant Surgeon, General Hospital, Calcutta. London, 1823.

7. *On Epidemic Cholera, Diarrhœa, and Cholera: their pathology and treatment, with a record of cases.* By George Johnson. London, 1854. Also by the same author: *Notes on Cholera, its nature and its treatment.* London, 1866.

8. *Epidemic Cholera.* Article on, in *Clinical Researches on diseases of India.* By Charles Morehead. Second edition, 1860.

9. *Cholera in its home. With a sketch of the pathology and treatment of the disease.* By John Macpherson, M.D., late Deputy-Inspector-General Bengal Army. 1866.

10. Article on *Epidemic Cholera* in *Reynolds's System of Medicine*, Second edition, 1870, by Edward Goodeve, Principal of Medical College, Bengal. Calcutta.

11. *A Treatise on Asiatic Cholera.* By C. Macnamara. London, 1870.

12. *A History of Asiatic Cholera.* By C. Macnamara. London, 1876.

13. *Annals of Cholera, from the earliest periods to the year* 1817. By John Macpherson. London, 1872.

14. *Asiatic Cholera, A history up to July* 15*th*, 1892, *causes and treatment.* By N. C. Macnamara. London, 1892.

15. *Asiatic Cholera: Its History, Pathology, and Modern Treatment.* By A. J. Wall, I.M.S. London, 1893.

CHOLERA
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CHAPTER I

HISTORY OF CHOLERA EPIDEMICS AND THEIR LESSONS

Records of Cholera prior to 1817

The first full and accurate accounts of cholera date from the great Indian outbreak of 1817, which was so widespread and fatal as to give rise to the impression that it was a new disease. This, however, was not the case, for in addition to possible references to cholera in ancient writings, we possess undoubted descriptions of the disease by medical members of early European expeditions to India. A full account of these will be found in John Macpherson's *Annals of Cholera from the earliest periods to the year* 1817, and it will suffice to mention here the following early references to the disease. Both Sanskrit writers of about 400 B.C. and Hippocrates give descriptions of outbreaks which may well have been cholera. The first undoubted descriptions, however, are by traders

with India, no less than sixty-six such references being enumerated by Macpherson between 1503 and 1817, ten of these were of epidemic character. Those of the sixteenth century were observed on the west coast, but in the seventeenth century the disease was reported from the east coast of India, the East Indies, and even from China. During the eighteenth century the affection was encountered in the ever-widening areas visited by Europeans. From 1781 to 1783 it assumed an epidemic form over a wide extent of country from Calcutta down the east coast through Gunjam to Madras, inland as far as Hurdwar, as well as in Burma: in fact over nearly all the parts of India of which we had a knowledge at that time. The only other epidemics in India between 1783 and 1817 were at Travancore in 1792 and the Mahratta country in 1794, after which there was a marked lull in the prevalence of the disease during the succeeding twenty-three years.

During the first three centuries after the discovery of India, cholera, according to Macpherson, visited Europe on several occasions. The first of these outbreaks was at Nismes in 1564, while during the seventeenth century cholera was said to be common in Europe as a sporadic disease but it never at all equalled the Indian outbreaks in malignity or extent. This supposed sporadic incidence in Europe is so unlike the behaviour of cholera in the nineteenth century as to throw some doubt on the last statement. It is generally agreed that there

was no important epidemic in Europe during the first half of the eighteenth century, and no cholera at all there in the second half and in the first two decades of the nineteenth century.

1817–23. Epidemic in India

The long lull in the prevalence of cholera was terminated by a terrible epidemic arising in 1817 in Lower Bengal, the home of cholera, and spreading during the next few years over all parts of India and to some neighbouring countries. This and subsequent outbreaks were most diligently investigated by N. C. Macnamara, who patiently searched the original records of the Calcutta and other Medical Boards, as well as the extensive literature of the subject, and embodied the results of his labours in a classical work on the *History of Cholera*, to which I am indebted for most of the following information. In order to avoid the wearisome string of places and dates which usually do duty for histories of this nature, I have embodied the main facts of the more important Indian and European outbreaks in a series of maps, and arranged the data in chronological columns, which allow the progress of the epidemics month by month to be seen almost at a glance. In the maps the large figures show roughly the areas invaded in the particular year, while the smaller numbers, such as 26–4, indicate the year and month of the nineteenth century in which particular places

were invaded. Thus, 26–4 stands for 1826, fourth month, namely April. After the chronological data of each epidemic a brief account of the principal investigations and the prevalent views as to the nature and prophylaxis of the disease is added, so as to allow of the gradual evolution of our knowledge of the subject being traced.

1817–23. Epidemic in India and Neighbouring Countries

It has been clearly shown by Macnamara that during the years preceding the 1817 epidemic the disease had not been completely absent from India, but was only in abeyance. Thus, when alarming reports of a serious outbreak were received from Jessore in August, 1817, the Calcutta Medical Board recorded their opinion that 'the disease is the usual epidemic of this period of the year, perhaps increased in violence by the peculiarities of the present season'. The rapid spread during this and the following year, and especially its terrible incidence in the Marquis of Hastings' army in Bundelkund in the North-West Provinces (now known as the United Provinces), soon revealed the unusually severe character of the disease, and led to full reports being called for from all parts of India, which for the first time furnished adequate data for an accurate description of cholera. The following synopsis will allow the principal features of this great epidemic to be readily grasped, so only points of exceptional interest will in addition be discussed.

1817: 8. Jessore (epidemic), Calcutta (pilgrims), Dacca and Rajshaye in Eastern Bengal.

„ 9. Purneah, Dinajpur, Balasore, and Cuttack in Orissa; Buxar, Chapra, Bhagulpur and Monghyr in Bihar (Western Bengal).

„ 10. Berhampur and Rungpur (Lower Bengal).

„ 12 and 1818: 1 and 2. Cold weather lull.

During 1818 epidemic cholera spread over the greater part of India in three main streams. (1) In a north-westerly direction through the North-West Provinces. (2) South-west through the Central Provinces into the Bombay Presidency. (3) Southwards along the east coast into the Madras Presidency. The months of the outbreaks in the principal places given below will serve to illustrate the progress of the epidemic.

	(1) *To the North-West.*	(2) *To the South-West.*	(3) *To the South.*
1818: 3	Allahabad (10,000 deaths)	—	—
„ 4	Chupra and Gorrackpur .	Saugor	Gunjam
„ 5	Azimghar, Oude, Nepaul	Nagpur	Vizagapatam
„ 6	Mutra	Bhopal, Kotah . . .	—
„ 7	Shahjahanpur, Agra, Delhi	Jaulna and Hyderabad .	Masulipatam
„ 8	Saharanpur	Surat (Bombay) . . .	Nellore
„ 9	—	Bellary (Western Madras)	—
„ 10	—	Bangalore	Madras City
„ 11	—	Seringapatam	Madura

1819. Cholera was still very prevalent over most of India, being especially severe in the Bombay Presidency, and was carried by ship to Mauritius.

1820. It reappeared in Bengal, parts of the North-west and Central Provinces, and in Madras.
1821. More localised, but prevalent in Lower Bengal, Madras, and Central India.
1822. The great epidemic had now subsided, the disease being seldom mentioned in the proceedings of the Medical Board this year, and was probably limited to the usual endemic areas during the next three years.

1821–3. Spread of Infection to Persia, Syria, and South Russia

1821 : 3. Cholera carried by troops from Bombay to Oman and Muscat in Arabia.
,, 7. Bunder-Abbas and Bahrein in the Persian Gulf.
,, 8. Bushire, Kazerum, and Shiraz, Jedz and Teheran, and to Resht in the Caspian Sea. Basra, where 15,000 died in eighteen days, it then spread up the Tigris to Bagdad.
1822. After a winter lull an outbreak occurred in the spring in the Tigris valley.
,, 8. In the Persian army at Ezerum, then spreading to Tabriz, Teheran, Ispahan, at a later date to Tauris, Tiflis, Resht, and Astrakan in South Russia.
,, 11. Aleppo by caravan across Syria.
1823. Recurred in Persia and the Caspian, and spread to Alexandretta and Antioch, but died out completely in the autumn of this year.

Prevalent Views on Cholera at the Time of the 1817–23 Epidemic

The information in the reports received from all parts of India regarding this epidemic were admirably summarized by the secretary of the Medical Board, Dr. James Jameson, in his work published in 1820, of which the following were the main conclusions. The proximate cause was a virus of unknown nature, producing purging and vomiting, followed by shock due to a primary action on the stomach and small intestine. The remote causes are unknown, irregular seasons and improper food not producing the disease. The spread might be connected with the east wind, which is always moist, but the spread along rivers was dependent on commerce. The disease prefers an alluvial soil. The board were of the opinion that the disease was not contagious, and quarantine was useless; but the removal of a camp to a new site often stopped the disease, this negativing contagion as a cause.

On the other hand, in a work published in 1826, Dr. R. Hartley Kennedy strongly held that cholera was typically contagious. Reginald Orton, in an essay published in 1820, concluded that cholera is due to deficient nervous action, brought about by lessened aeration of the blood, which is dependent on unsettled weather consequent on deficient electrical fluid in the atmosphere. In 1825 Annesley's work appeared, which contains a most

careful and accurate description of the disease and its treatment, and one well worthy of study even at the present day (see page 159). He speculates but little on causation, but thought the great epidemic was connected with the prevalence of very unusually disturbed seasons in Madras for several years before its appearance, while sudden exposure to cold was the most common exciting cause.

These wide divergencies of opinion are only natural in the face of such a sudden and widespread outbreak, but according to Macnamara the records collected by the Medical Board are the only complete ones ever obtained from all parts of India, and are consequently worthy of careful consideration. It is also of great interest to note that when a very serious outbreak of cholera appeared in the Marquis of Hastings' army in Bundelkund, that nobleman marched his troops across country away from the river on whose bank he was encamped at the time, and had the satisfaction of leaving the disease rapidly behind him. This is the first mention I know of the adoption of a procedure which has so often proved of great value in India. There is no mention, however, in Macnamara's account of Hastings having marched at right angles to the wind, as was later ordered in the government army regulations up to a comparatively recent date.

1826–37. Epidemic in India, Persia, and Europe. (Map I)

This is the first great spread of Asiatic cholera to Europe of which we have detailed records. Owing to the slowness of communication at the time of its occurrence the spread of the disease can be easily traced from one country to another, as illustrated by Map I, which includes most of the following data.

1826: 4. Epidemic from Calcutta to Dinapur in Behar.
„ 5. Benares (two or three hundred deaths a day). Baroda.
„ 6. Cawnpore (severe among the troops).
„ 11. Agra, Mutra, and Delhi.
1827: 1–3. Recurred in epidemic form in Calcutta and over all Lower Bengal.
„ 5. Agra (very severe), Bareilly, Meerut, and Moradabad in the North-West Provinces. Nasirabad in the Central Provinces.
„ 6. Sabathu near Simla. Ajmere and Jeypur in Rajputana.
„ Hardwar fair and throughout the Punjab in latter part of 1827.
1828. Prevalent in Afghanistan.
1829. Persia infected through Herat to Khorassan and Teheran. Also spread to Bokhara and Khiva.
„ 8. Orenburg in Russia from Khiva, or by travelling Kinghis tribes.
1830: Spring. Khorassan and Tabriz in Persia and to Resht and Baku on the Caspian.

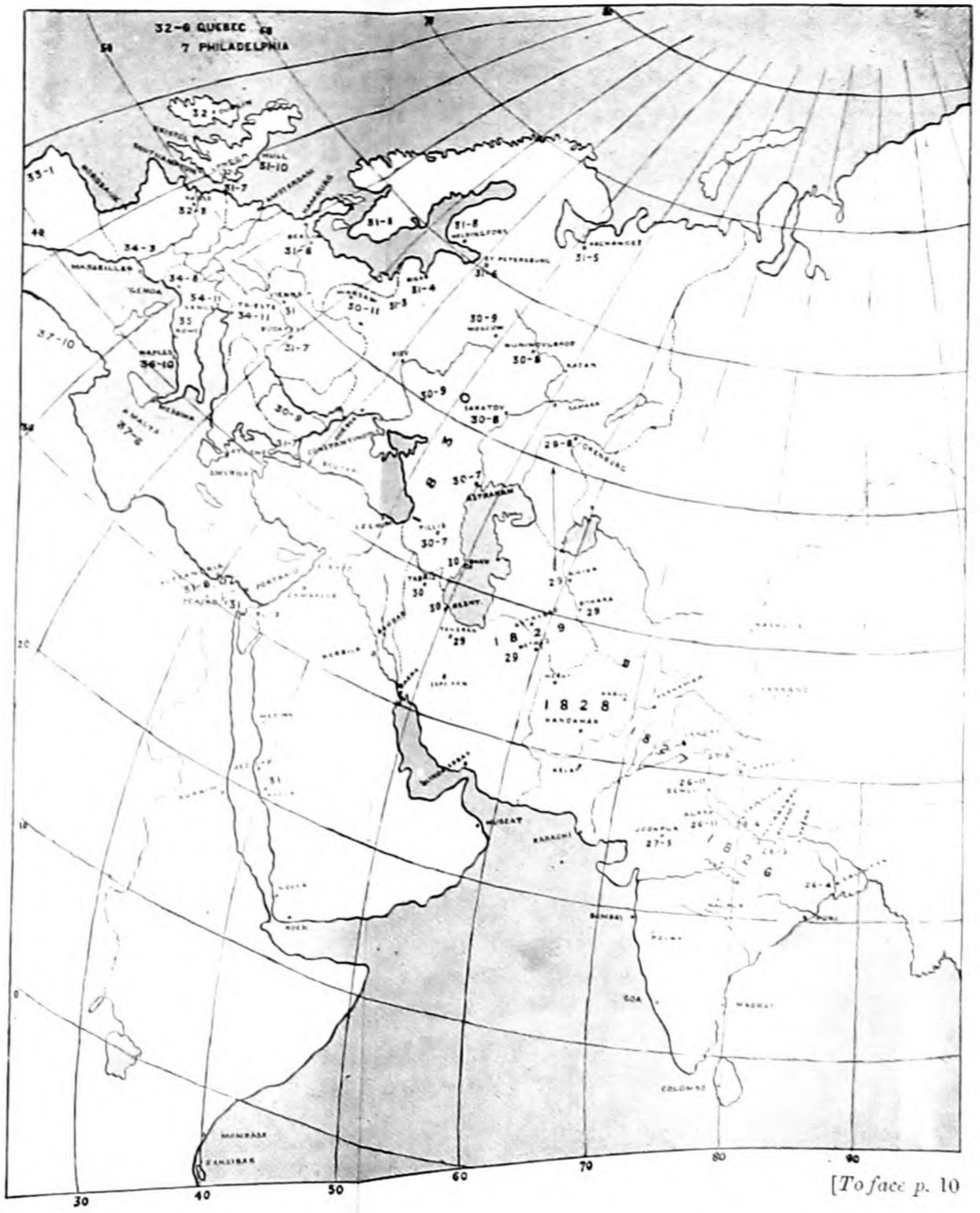
1830: 7. Tiflis and Astrakan.
„ 8. Saratoff (2,367 died) and Nijni Novgorod.
„ 9. Kharkoff and Moscow. Bulgaria and West Russia.
Winter lull, during which cases persisted in the Russian army in Poland.
1831: 4. Grodo, Vilna, Warsaw, and Riga. Severe in troops in Poland.
„ 5. Archangel.
„ 6. St. Petersburg.
„ 8. Helsingfors, Sweden, Berlin, Vienna, and Bohemia.
„ 7–10. In English ships in the Medway from Riga.
„ 10. Sunderland and spread to Newcastle, Gateshead, and Edinburgh.

The south-east of Europe was also separately invaded this year from Arabia as follows:

1831. Severe outbreak at Mecca, where half the pilgrims died. Spread by them to Suez, Cairo, and Asia Minor.
„ 7. Constantinople, Bulgaria, and Galicia to Cracow.
„ 8. Alexandria.
1832: 2. London. (4,000 deaths in all occurred in Great Britain in this epidemic.) Later in the year Hull, York, and Leeds were attacked.
„ 3. Paris (7,000 died in eighteen days). Ireland, where it spread widely.
„ 6. Quebec and Montreal by ship from Dublin. New York.

MAP I, 1826–37

Epidemic in India, Afghanistan, Persia, Europe and America



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1832: 7. Philadelphia, and by the end of the year widely over the United States and Canada.
1833: 1. In Portugal, at Oporto, by ship from England. Spread to Spain, in spite of quarantine, being severe there in the autumn.
„ 2. Havana, where 8,253 died out of 65,000 inhabitants.
Later in Mexico, where 15,000 died.
1834: 3. Severe in the South of France, Nice and Cannes being infected in June.
„ 8. Turin and Genoa.
„ 11. Venice, Trieste, and all Northern Italy.
1835. Recrudescence over all Italy.
1836: 4. Milan and the Dalmatian coast.
„ 10. Naples and Ancona in Sicily.
1837: 6. Malta (4,000 deaths).
Recrudescences also occurred in this year in Italy, Marseilles, Berlin, and England, but the disease died out completely in 1838, no Asiatic cholera appearing in Europe between 1838 to 1846.

Prevalent Views on Cholera during the 1826–37 Epidemic

This terrible and widespread epidemic of cholera presents many points of interest. In the first place it will be observed that the disease took five years to spread from Lower Bengal to European Russia (Map I), while in the epidemic of 1892 it reached Russia by the same route in as many

months (Map VI), in accordance with the greatly quickened methods of communication at the later period. In the absence of rapid steamship and railway services in the early part of the nineteenth century, the disease spread slowly overland along the lines of communication by caravans and the movements of troops, wars in Persia and Poland aiding its diffusion. When the epidemic reached Europe very severe quarantine methods were put in force in various countries to combat its progress, but without avail. Troops were freely used, but triple cordons failed completely, and even the death penalty for infringement of the regulations in Spain was equally futile.

In Europe various views regarding the mode of spread were held, the air-borne theory receiving much support. The western extension of the disease elicited two new works on cholera by experienced Anglo-Indian writers. Frank Corbyn's treatise appeared in 1832, and is chiefly noteworthy for his strong advocacy of large doses of opium and calomel in combination, together with the inevitable bleeding of those early days, while he severely condemned the use of stimulants. He agreed with the writers already referred to in regarding climatic variations and chills as important factors in producing outbreaks of cholera, but he attributed its capricious distribution to local generation of the poison due to a peculiar state of the soil, as suggested by Sydenham. He considered that the poison acted by suddenly checking per-

spiration, thus inducing internal congestion followed by inflammation. The work of William Twining, issued in 1833, is an admirable clinical study with clear indications for the treatment of the different stages, and includes remarks on the dangers of venesection, fond as he was of that measure in fevers. He laid stress on the relation of the symptoms to cessation of the functions of the organs supplied by the great solar plexus, which is probably too little borne in mind at the present day. He also regarded the immunity of hospital servants as conclusive evidence of cholera not being a contagious disease in the correct sense of that term. It should also be mentioned that during this epidemic intravenous injections of saline solutions appear to have been extensively used for the first time by Drs. Mackintosh and Latta in Edinburgh, but without much success.

1830–45. Epidemics in India

In addition to the yearly endemic prevalence of cholera in Lower Bengal and some other parts of India, the following are the most important epidemics during this period :

1831	Severe epidemic in Bengal spreading to Central India.
1832–3.	Epidemic in Central India, Madras, and Bombay spreading to Mecca in 1835; this perhaps originated the Mediterranean outbreak of 1836–7.

1838 Epidemic in Bengal and very severe in the North-West Provinces. Carried to Quetta and Kabul in 1839 during the Afghan War.

1840 Epidemic in Lower Bengal only and carried by troops to China (see below).

1842 Severe all over Bengal only.

1840–9. INDIA, CHINA, AND EUROPEAN EPIDEMIC. (MAP II)

According to Macnamara's account, this epidemic is a unique example of the spread of cholera from India to Europe by the roundabout way of Singapore, China, and Chinese Turkestan, to Afghanistan, Persia, and Europe, as will be seen from the following synopsis and Map II:

1840 Outbreak in Singapore carried by Bengal troops from Calcutta.

,, 3. Among troops at Chusan in China, and afterwards became epidemic.

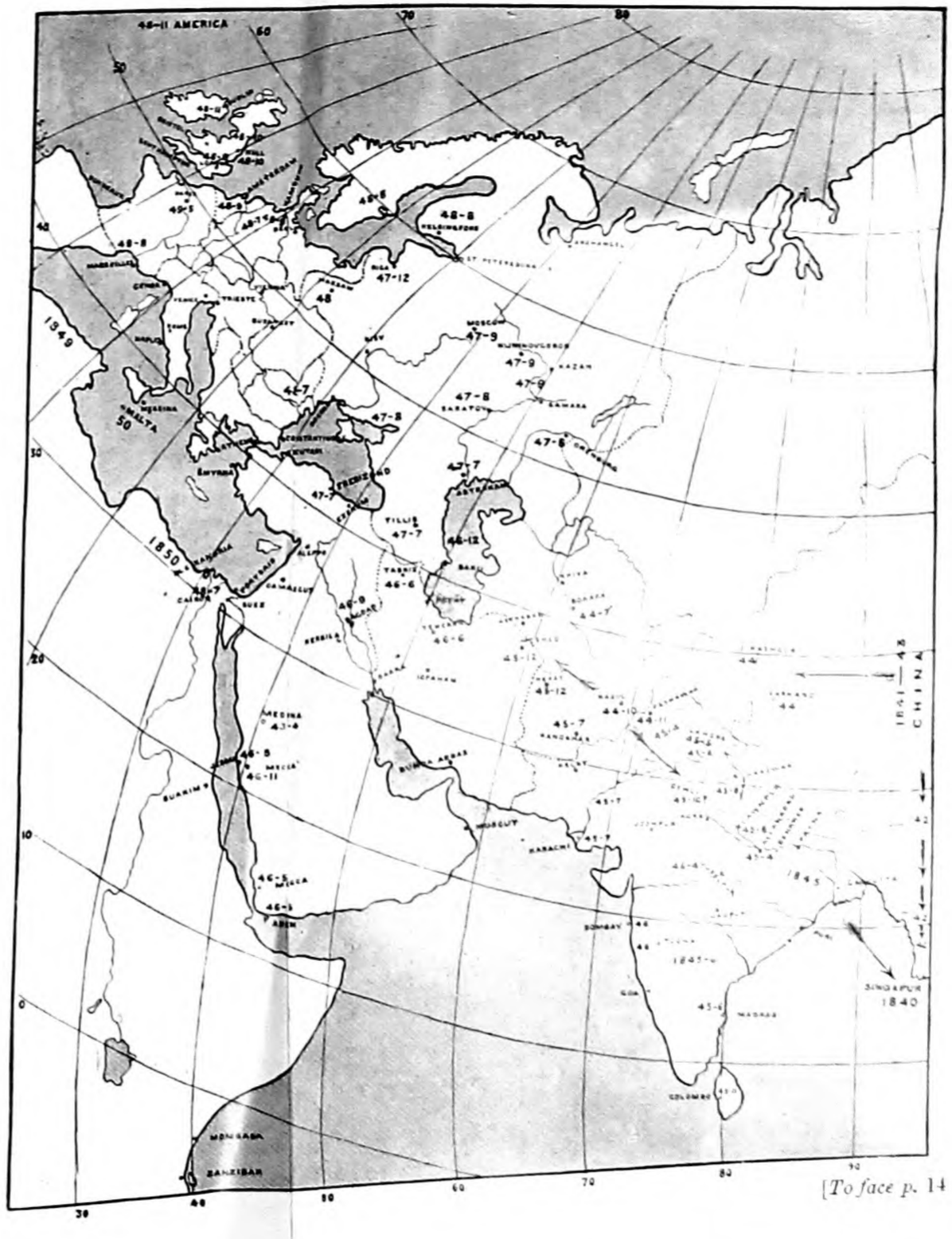
1841: 3. Among the troops in China, especially in the Yang-tse-kiang Valley. Severe at Pekin and Canton, and carried to Manila.

1842 Appeared in Upper Burma, from Yunnam through Bhamo, and spread south to Ava, and down the Irawadi River.

1844 Reached Yarkand in Khotan and Kashgar in Chinese Turkestan by the main trade routes westward from China.

MAP II, 1840–9

EPIDEMIC IN INDIA, CHINA, EUROPE AND AMERICA



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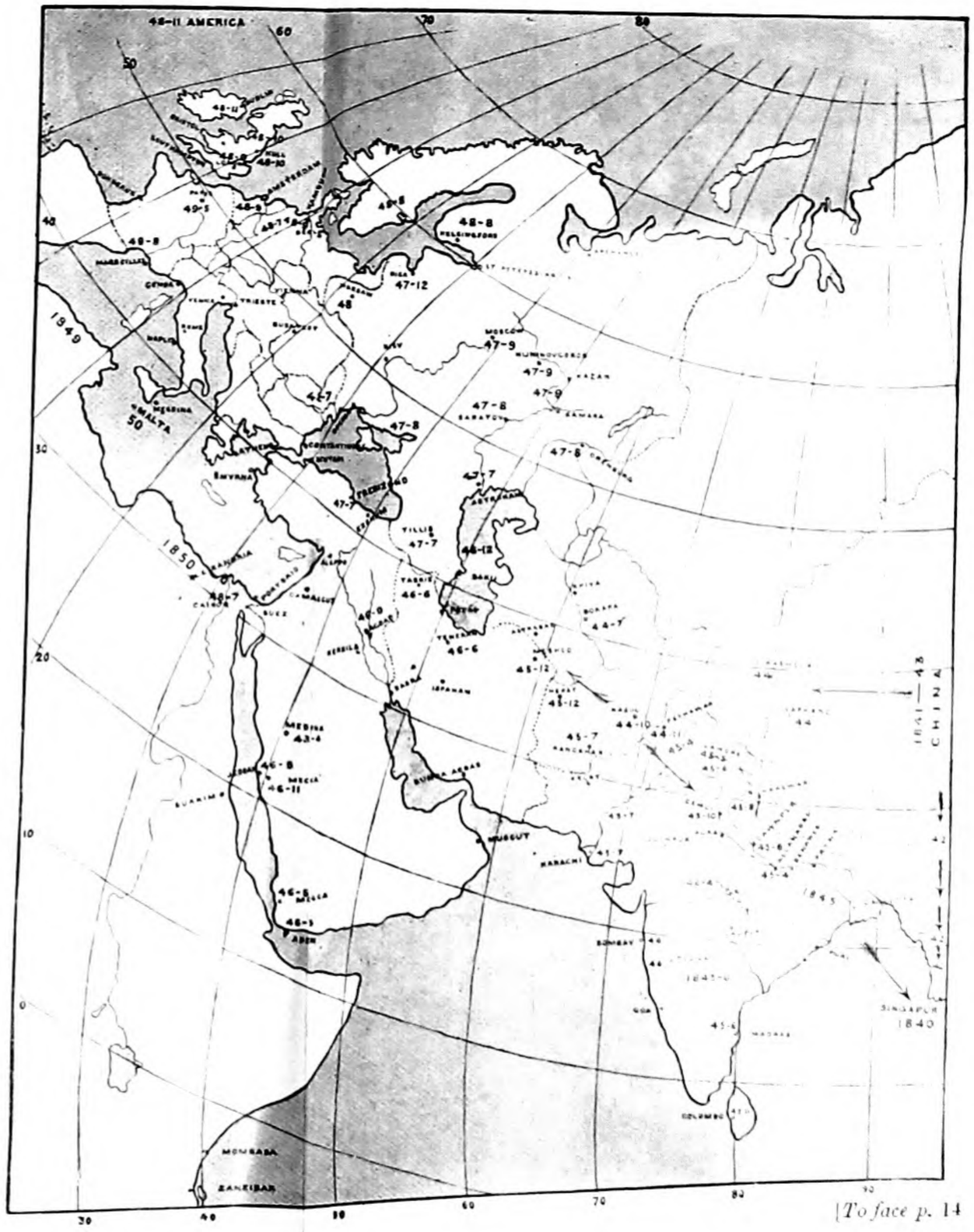

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1844: 7. Spread further west to Bokhara and Balkh in Russian Turkestan (25,000 died).
,, 10. Kabul from Bokhara.
,, 11. Peshawar from Kabul.
1845: 4. Jhelum, to the east of Peshawar.
,, 5. Lahore (east of Jhelum) (22,000 deaths).
,, 6. Umritsar, Ferozepur, Loodiana, Central India, and Sukker on the Indus.
,, 7. Hyderabad, Scinde, and Karachi.
,, 8. Meerut.
,, 10. Delhi.

Thus the Punjab was invaded and overrun by cholera from the west, while the disease also spread down the Indus to Karachi. There was no cholera in the North-West Provinces (United Provinces of to-day) this year from which the above outbreak could have been derived. The disease had thus travelled from Bengal to China and back to the north-western part of India through Afghanistan; a reversal of its usual course from the Punjab westward to Kabul.

In the meanwhile the epidemic continued its regular westerly course as follows:

1845: 7. Kandahar very severely attacked.
,, 12. Herat and Meshed in Persia.
1846: 6. Recurred in Meshed, and spread to Teheran and Tabriz.
,, 9. Bagdad and up the Tigris and Euphrates to Diarbekr and Urfah.
,, 11. Mecca, among the pilgrims (15,000 deaths).
,, 12. Derbend, on the Caspian Sea.

In the meanwhile cholera was very severe in Lower Bengal in 1845, and spread to Madras. In 1846 it recurred early in Madras, and in April overran Bombay and Western India, as well as the Central Provinces. In May it was carried to Aden, and thence spread to Mocha, Jeddah, and Oman in Arabia. It was probably this second stream which infected Mecca and the Euphrates Valley in 1846, and reinforced the original one spreading west from Afghanistan.

1847: 4. Recurred at Derbend.
„ 7. Tiflis and Astrakhan, via Poti to Trebizond (Black Sea), over the Caucasus by the military road to Stavrapol.
„ 8. Taganrog on the Sea of Azoff, and up the Volga to Saratoff and Orenburg.
„ 9. Simbirsk, Nijni-Novgorod, and Moscow.
„ 10. Constantinople.

During the winter lull, only sporadic cases occurred in South Russia.

1848: 4. Among pilgrims at Mecca and Medina, who carried it to Egypt.
„ 7. Severe in Egypt and Berlin.
„ 8. Moldavia, Wallachia, all Russia, Poland, Finland, and Sweden.
„ 9. Hamburg and Holland. London and the Thames bank from Hamburg.
„ 10. Edinburgh, Hull, and Sunderland from Hamburg.

1848: 11. Belfast from Edinburgh. Staaten Island (New York) and New Orleans, spreading up the Mississippi to Cincinnati.

Winter lull in Europe and America.

1849 Recurred over most of Europe and North America, including Canada. Severe in the South of France; 15,677 deaths in Paris up to the end of June. Widely diffused over England, and severe at Hull.

,, 5. New York, and all over the United States.

,, 8. Marseilles, Toulon, Nice, Naples, and Brindisi.

,, 11. Tunis, Oran, and Algeria.

1850 Severe in Egypt and the North African coast of the Mediterranean. Slight outbreaks in Europe and America. Malta and Gozo attacked. Spread over Mexico and California, invading Cuba and Jamaica.

1851 Only a few cases in Eastern Europe. Recurred in Cuba and Jamaica. Canary Islands infected from Havana.

Prevalent Views on Cholera during the 1840–9 Epidemic

This epidemic was one of the most terrible and widespread on record. In 1847 to 1849 it is estimated that the deaths in Russia alone exceeded one million, no less than 471 towns having been

attacked. In England there were 53,293 deaths recorded, the mortality in Hull having reached 24·1 per mille of the inhabitants. The disease appeared in 119 places, spreading in an apparently capricious manner. Dr. Farr, however, clearly showed that the incidence was highest on low-lying places, and decreased with increasing elevation above high-water sea level, the affection being thus favoured by a humid soil. Still more noteworthy were the views advanced at this time by Drs. Snow and Budd. In 1849 Snow published his conclusions that cholera depended upon a specific poison contained in the stools and vomited matter of patients suffering from the disease, which when swallowed by a susceptible person was reproduced in increasing quantity in their intestine. He further held that the infected discharges gained access to the drinking water of wells and rivers through a faulty drainage system, and thus reached the alimentary canals of other people and infected them with the disease. William Budd, of Bristol, suggested that the disease was due to a special living organism of a fungus nature, which multiplied in the intestine and excited the copious evacuations of cholera. He believed the organisms were disseminated by food and especially by water, and recommended destruction of the poison in the evacuations by chemical disinfectants, such as sulphide of iron and chloride of lime. The safe guarding of drinking water was the principal means of preventing

the spread of the disease. A German observer, Dr. Boelm, had indeed described forms of fungoid growth in cholera stools as early as 1838, which he considered to be the cause of the disease. It was undoubtedly the views of Snow and Budd which paved the way for the accumulation of conclusive evidence in favour of their water-infection theory during the succeeding European epidemics. Their views at this time were held to be untenable by Drs. Baily and Gull in a report on the 1848–9 outbreak to the Royal College of Physicians, issued in 1856, in which these well-known physicians maintained that cholera is spread independently of communication between the sick and the healthy, and they concluded that the agent most likely to have conveyed the poison from one spot to another is the wind.

1848–53. India, Persian Gulf, Europe and America. Map III

1848: 5. Dinapur in Behar.
„ 8. Cawnpore and Agra, but none further west.
1849: 5. Patna, Tirhoot, Mirzapur, and Allahabad.
„ 7. Puri in Orissa, among pilgrims. Cawnpore, Jubelpur, Saugor, and Nursingpur in the Central Provinces. Ahmednagar and Poona in Bombay Presidency.
„ 8. Bombay Island.

1850: 8. Recurred over Bengal and in Assam, and was very severe in Madras and along the western coast of India.
1851: 6. Appeared at Basra at the head of the Persian Gulf.
,, 7. Up the Euphrates to Hilleh (1,000 deaths).
,, 8. Bagdad (1,847 deaths), spread by Persian pilgrims.
1852: Spring. Recurred at Bagdad, and spread up the Tigris.
,, 10. Tabriz (12,000 deaths), and spread east towards Teheran.
,, 11. Erivan in Transcaucasia.
1853: 5. Teheran (15,000 deaths), and all Northern Persia.

NOTE.—Cholera was also epidemic in the Punjab in 1852, and may have spread to Persia in 1853, reinforcing the former current through the Persian Gulf.

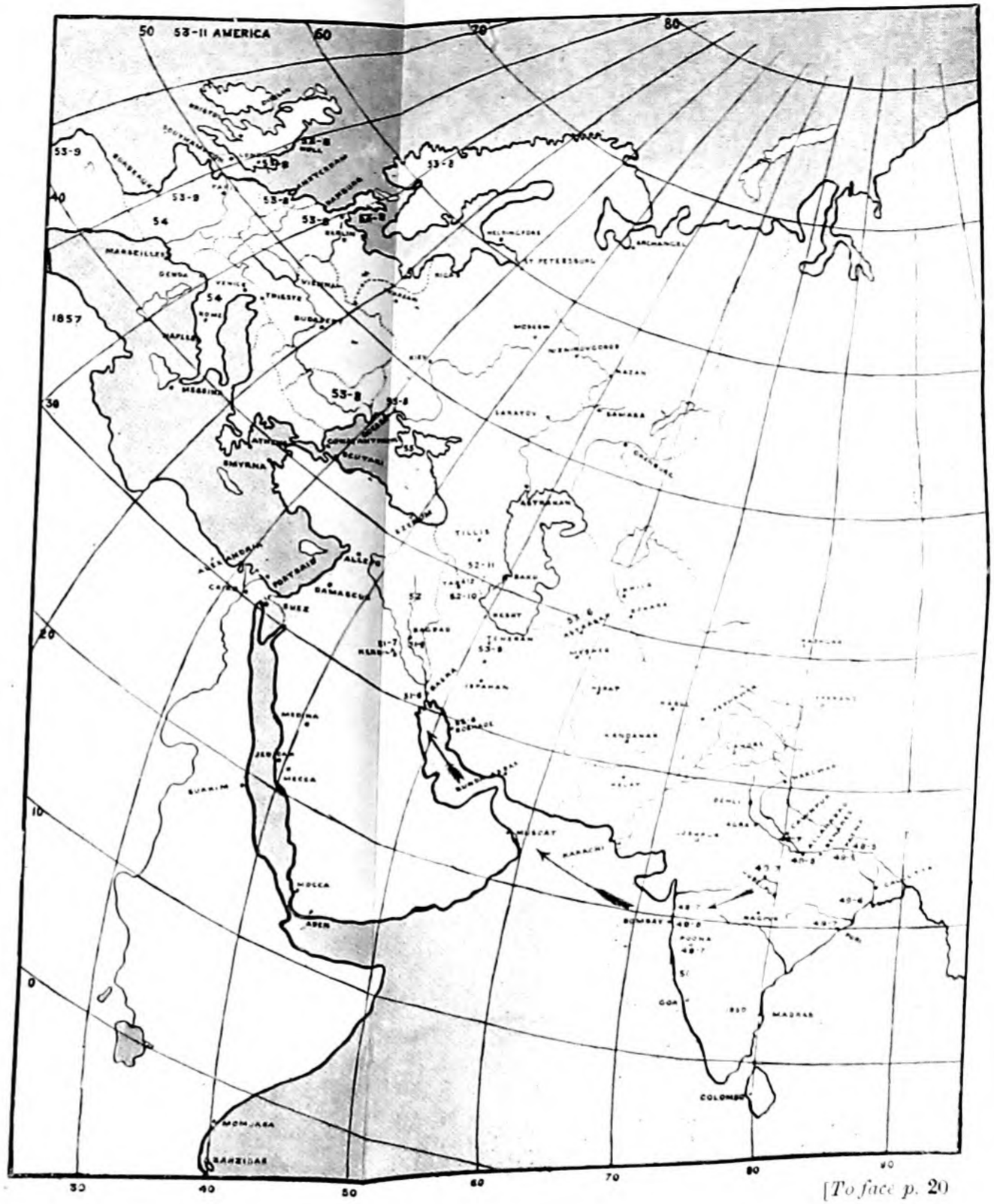
1853: 6. Astrabad, Bushire, Shiraz, Hamadan, and Kermanshah.
,, 10. Basra reinfected by troops.
,, 11. Bagdad.

CHOLERA IN EUROPE

1853: 8. Odessa, Jassy, Moldavia, Wallachia, Copenhagen, Norway, North Prussia, Hanover, Holland, Newcastle, and Gateshead.
,, 9. London, Piedmont, and Portugal.
,, 10. France.

MAP III, 1848–53

EPIDEMIC IN INDIA, PERSIAN GULF, EUROPE AND AMERICA



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1853	By the end of the year the disease had also spread to New York, New Orleans, Mexico, and all the West Indies.
1854	Recurred in virulent and widespread form in Asia, Europe, and America, as the most deadly outbreak yet experienced. The mortality was 20,000 in England, 140,000 in France, 24,000 in Italy, while many other countries suffered severely.
1855	Recurred over all Europe and much of America and the West Indies. In Russia it was practically endemic, and attacked the troops in the Crimea. Scattered cases occurred in Great Britain and France.
1857–58	Cholera died out of most of Europe and America, but during 1857 it recurred in several places; Hamburg suffered severely, and a few cases were seen in England. Algiers and Morocco were also invaded.

The most noteworthy feature of this great epidemic was the rapidity of its spread once it reached Russia in 1853. It was carried in a few months all over Europe and America, owing to the greatly increased rapidity of communications, which made it increasingly difficult to trace its exact course from place to place.

Quarantine and Inspection. By the time of this outbreak the futility of rigid quarantine systems, especially as regards overland communications,

had become widely recognized, and they were much less resorted to than on the former occasions. Greece, in 1832 and 1849, had been able to protect herself by such measures, on account of her peculiarly isolated position, but was prevented from doing so on this occasion through being occupied by a foreign Power. In England, Dr. Simon introduced the system of inspecting all vessels arriving from infected ports, isolating any suspicious cases, and keeping a watch on the remainder, who were allowed to land. In thirty-two out of forty-two instances in which the first case was isolated and disinfection carried out, the epidemic did not develop. The method thus proved at least as successful as full quarantine, without the disadvantage of completely dislocating trade, and its great value is testified by the fact that it has for some time been the most generally accepted preventative measure against the invasion of Europe by cholera.

Water Supplies and Cholera. The writings of Snow and Budd in 1849 now began to bear fruit in the closer investigation of the possibility of infection being conveyed through drinking water, with the result of greatly strengthening the theory. Dr. Snow himself worked out the famous Broad Street outbreak, in which a well was contaminated by a leaking cesspit, into which the stools of a cholera patient had passed. Within the next few days several hundred cholera cases occurred among the surrounding persons who drank the

water from this pump, while two ladies in a distant part of Hampstead who had consumed water taken from the same pump, also contracted the disease. Nevertheless, so strongly was the air-infection theory held, that a scientific committee reported that the contamination of the well water was more likely to have taken place from the atmospheric infection of the district than from the specifically infected and leaking cesspit only three feet from it.

Again, in Newcastle the deaths had reached 140 a day when it was found that the water company had been supplying unfiltered water taken from the river at a point to which the sewage of the city was carried up by the tide. On this supply being stopped, the outbreak rapidly declined. An even more striking demonstration was furnished by the cholera death-rates varying from 37 to 140 per thousand among similar classes of the inhabitants of London, who were supplied with drinking water by two different companies. The lower rate was among those furnished with a pure water by the Lambeth company, although in the previous outbreak in 1849 the same population had suffered more than three times as much from cholera, their water having been impure at the earlier period. The highest rate in 1853–4 was among the drinkers of the impure Thames water supplied by the Southwark and Vauxhall company. These striking facts led to the passing of the Metropolitan Water Supply Act, which has made London the

most healthy of the great cities of the world; and thus these terrible visitations of cholera have doubtless ultimately resulted in the saving of many more lives than they destroyed during their prevalence, through educating public opinion to the point which allowed sanitary reformers to be listened to with the respect they merited.

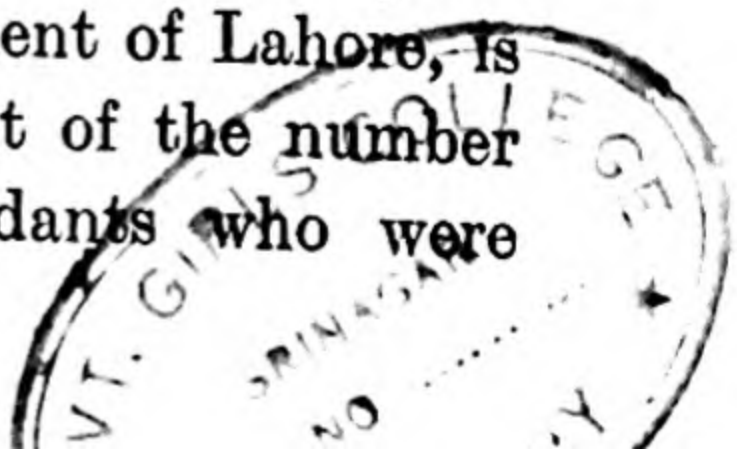
Current Views on Cholera. After this outbreak, a sanitary conference was held at Paris, whose conclusions agreed closely with those of Baily and Gull, already referred to, and recommended general measures of hygiene and cleanliness, plenty of fresh air, and disinfection of buildings and merchandise. It was also at this period that Professor Pettenkofer of Munich put forward his famous theory of a damp porous subsoil impregnated with organic excrement, as a local necessity for the epidemic propagation of the ferment of cholera; the infection taking place through the air from the contaminated soil, especially during a rise of the ground-water level. With regard to the treatment of the disease, the most noteworthy departure was the advocacy by Dr. George Johnson of large doses of castor oil to eliminate the poison by the bowel, although it was not until a decade later that his views appear to have attracted much attention. A valuable clinical account of cholera has also appeared in Charles Morehead's *Clinical Researches on Diseases of India in* 1856.

1855–62. Epidemics in Asia and Africa

During the next few years Europe was spared epidemic cholera, although on several occasions it was widespread in Asia. In 1856 the disease overran Northern and Central India, including the Punjab, and also reached Bombay and Madras. In addition, it was widespread in Persia and the Euphrates valley during 1856, and recurred there in the following two years. In fact, according to Macnamara, cholera was endemic both in Persia and in parts of Russia throughout the decade 1851–61.

In 1858 it was carried from Aden to Berbera on the west coast of the Red Sea, and travelled south to Somaliland and nearly all the East African coast towns, as far down as Mozambique. At Zanzibar no less than 7,000 died out of a population of 20,000.

In 1860 cholera was again widespread from Bengal through Central India to Bombay, but a famine-stricken tract in the North-West Provinces escaped the visitation in a remarkable manner. In 1861 cholera was again terribly prevalent all over India, including the North-West Provinces, where rain had now fallen. The Punjab was especially affected, while the disease spread to Kabul. In the following year cholera was carried to Pekin, where 15,000 persons were said to have perished. A terrible outbreak this year among the troops at Mian Mir, the cantonment of Lahore, is especially noteworthy on account of the number of European soldier sick-attendants who were



attacked while on duty in the cholera wards, all of whom, however, were derived from infected regiments. On the other hand, all of the medical officers, native servants, or sick attendants, none of whom would eat or drink in the hospital, escaped. Nevertheless, a commission, presided over by a high civilian official, reported, contrary to all previous experience, that the hospitals had been the most direct cause of the dissemination of the disease, and that water was not a vehicle of infection. Two of the four commissioners, including the medical officer, dissented, yet this report unfortunately strengthened the government in their policy of regarding cholera as an uncontrollable disease, and adopting a policy of doing nothing. The inquiry did some good by leading to the establishment of a sanitary department in India, which has ever since published voluminous reports, although it has been much restricted in effecting a corresponding amount of practical reform by lack of sufficient funds and executive powers.

1863–6. Epidemic in India, Arabia, and Egypt, spreading to Europe and America, as well as to Africa in 1868–9. (Map IV)

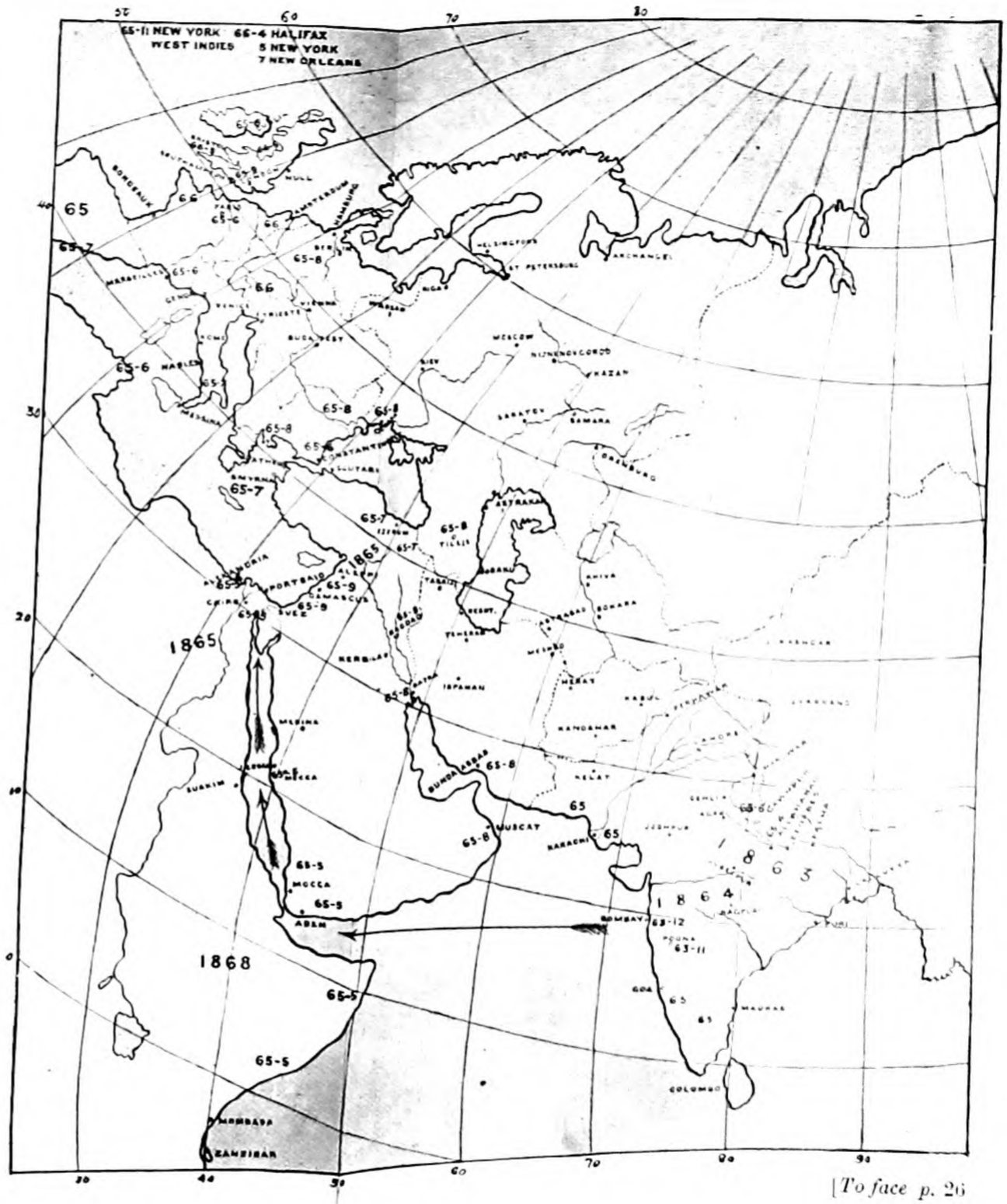
1863 Very severe epidemic all over Bengal and the North-West Provinces up to Agra. Widely disseminated by pilgrims from Allahabad.

,, 7. Lucknow (2,000 deaths).

,, 11. Poona, by pilgrims from Punderpur.

MAP IV, 1863–6

EPIDEMIC IN INDIA, ARABIA, EGYPT, EUROPE AND AMERICA, AS WELL AS TO AFRICA IN 1868–9



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1863: 12. Bombay.
1864 Recurred in Bengal, and spread over the Central Provinces and Berar to Western India; 4,588 deaths during the year in Bombay city.
1865 Spread down the Malabar coast to Bellary and Mysore, causing 40,000 deaths. Very severe in the Bombay presidency, 84,000 deaths being registered. Travelled northwards to Karachi, and then westwards along the Mekran coast of Baluchistan.
,, 5. Aden, Mocha, and Makalla to Mecca, where 30,000 out of 90,000 pilgrims are said to have died. Spread by the pilgrims via Jeddah to Suez.
,, 6. Spread from a fair at Berbera down the east coast of Africa. Alexandria by rail from Suez, and all over Egypt (60,000 deaths). Constantinople, Allepo, Beyrout, Damascus, and all over Syria, from Suez by pilgrims.
,, 7. Reached Cyprus.
,, 8. Muscat, Bunda-Abbas, and Basra on the Persian Gulf, and up the Euphrates to Kerbella, Hillah, and Bagdad. (Nil in North Persia or the Punjab.)

In Europe

1865: 6. Constantinople, Marseilles, Toulon, Paris, and Malta in the lazaretto.
,, 7. Trebizond and Ezerum on the Black Sea, from Constantinople. Ancona in Italy from Alexandria. Gibraltar,

by troops from Malta. Valencia in Spain, from Marseilles, with 5,100 deaths. By December, 31 of the 49 Spanish provinces were attacked.

1865: 8. Tiflis, in the Caucasus, Bulgaria, Salonica, Odessa, from Constantinople, and Altenburg in Germany, from Odessa.

,, 9. Wardau from Altenburg, Southampton from the Mediterranean, and Weymouth from Southampton.

,, 10. Gaudaloupe, through clothes from Bordeaux.

,, 11. New York, in quarantine station only.

1866 Recurred among the Mecca pilgrims and all over Europe, spreading to St. Petersburg, Bavaria, Saxony, Belgium, Holland, and the north of France. The armies of Prussia, Austria, and Italy suffered much. The Mediterranean coast largely escaped.

,, 4. Halifax, in Canada, by ship from Liverpool.

,, 5. Bristol and Liverpool (1,792 deaths), from Rotterdam. Southampton from Alexandria. New York and all over the United States.

,, 7. London (4,000 deaths). Dublin from Liverpool, and scattered cases elsewhere in England. New Orleans and up the Mississippi.

1867 Rapidly subsided in Europe, although still present in Turkey and slightly in Russia. Extended to Argentina and British Honduras.

1868 Completely died out of Europe. Appeared in Abyssinia, Central and East Africa, and for the first time affected Senegal on the west coast.

1869 Zanzibar.

The most important feature of this outbreak was the rapid diffusion of the disease by pilgrims. This took place first in 1863 from the great Allahabad fair in the North-West Provinces; and secondly, in 1865, at the time of the terrible dispersion of the cholera-stricken pilgrims from Mecca which carried the disease during the single month of June to Egypt, the east coast of Africa, Syria, Constantinople, and a number of Mediterranean ports. The epidemic thus originated ultimately overran all Europe and most of America.

The principal hygienic lessons were again derived from English experience, for it was demonstrated that in the area supplied with the insufficiently purified River Lea water of the East London Water Company, the death-rate from cholera was 72 per 10,000 inhabitants, although among the consumers of the seven other London water companies the rate varied only from 3 to 8 per 10,000.

1866–70. Epidemic in India, Afghanistan, Persia, and Europe. (Map V)

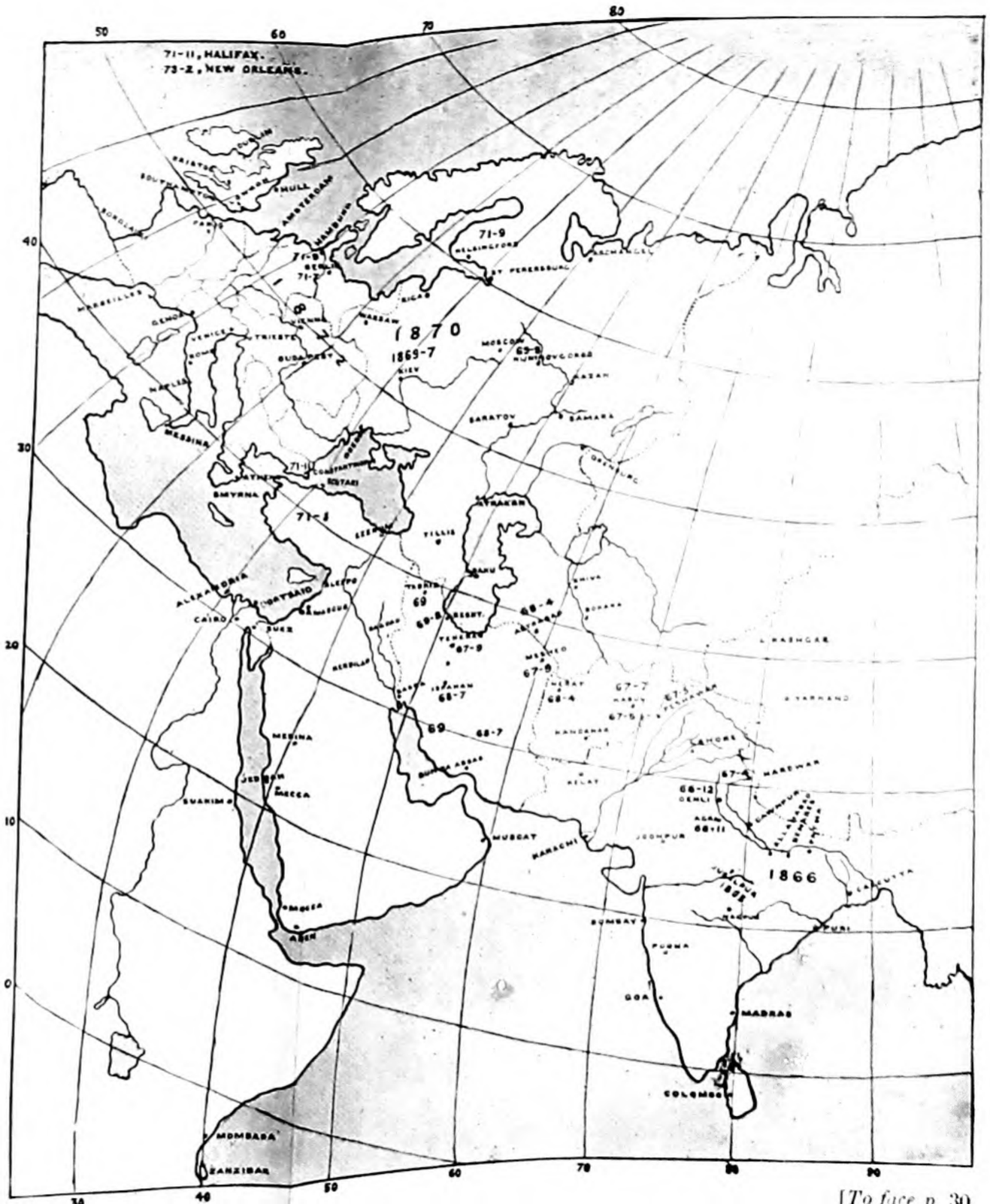
1866 Endemic in Bengal early in the year. Jodhpur (Central India), in July.

„ 11. Agra, severe in the Viceroy's durbar camp, and spread to Meerut.

1866: 12. Rookee and Delhi.
1867: 3. Allahabad, Benares, and Bhurtpur.
,, 4. Hardwar, among the pilgrims, who spread it widely on dispersing.
,, 5. Peshawar and Kabul, through pilgrims.
,, 7. Severe in Afghanistan (8,000 deaths in Kabul alone).
,, 9. Meshed and Teheran.
1868: 2. Mazanderan Province of Persia.
,, 4. Meshed, to Astrabad and around Herat.
,, 7. Epidemic among pilgrims at Meshed, and carried by them to Yedz, Kirman, and Ispahan in Central Persia.
1869 Spread further west in Persia to Shiraz in the south, and Tabriz in the north-west.
,, 8. Astrabad and Resht on the Caspian Sea, and to Kiev in Russia, by Persian pilgrims.
,, 9. Nijni Novgorod fair.
1870 Very severe in Russia. Carried by raftsmen along the Vistula to Prussian Poland.
1871: 7. Prussia.
,, 8. Asia Minor.
,, 9. Hamburg and Finland.
,, 11. Constantinople. Halifax in Canada.
1872 Widespread in Europe, especially in Austria, Hungary, Roumania, Prussia, and Belgium. Sporadic cases only in England.
1873 Much less severe in Europe, but present in Russia and the Netherlands.
,, 2. Carried to New Orleans and up the Mississippi.

MAP V, 1866–70

EPIDEMIC IN INDIA, AFGHANISTAN, PERSIA AND EUROPE



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After the above epidemic, the second cholera congress assembled at Vienna in 1874. They were of the opinion that cholera is spread from India by human intercourse through drinking water, soiled linen, and merchandise, the incubation period being only a few days. They recommended medical inspection of all ships from infected ports, those with infection only being detained, and their cargo and the clothes of the passengers being disinfected, any sick being first removed to isolation hospitals. A small commission also drew up quarantine regulations for those States who intended to carry out that measure, the period of detention for surveillance of vessels from infected ports extending to seven days.

1879–83. Epidemic in India, Egypt, and Europe

By this time railways had been extended so widely over India that the increased rapidity of communications made it frequently impossible to trace minutely the spread of cholera, thus only the broad outlines of this and the following epidemic can be given.

1879: 4. On April 12 cholera appeared among the 3,000,000 pilgrims at the great Kumbh fair at Hardwar, which takes place every twelfth year. The pilgrims rapidly dispersed, and by April 15 had carried the disease as far as Lahore, a distance of

250 miles, soon after it reached Peshawar in the extreme north-west of the Punjab. Later in the year it invaded Cashmir and Afghanistan.

1880 Severe in Oude and the North-West Provinces.

1881 Severe in Bombay, and carried by pilgrim ship to Aden.

„ 8. Mecca (6,000 deaths), and carried by pilgrim ship to Suez, where quarantine was successfully enforced.

1882: 7. Aden, among Afghan pilgrims from Bombay.

„ 10. Mecca.

1883: 6. Damietta, Rosetta, and Port Said, and all over Egypt. Especially severe at Cairo and Alexandria; 50,000 died in Egypt this year.

1884: 6. Toulon and Marseilles and the South of France. Genoa, Naples, Palermo, and other places in Italy. Slight in the Spanish ports in communication with French ones.

1885 More severe in Spain. Finally died out of Europe again in 1887.

Scientific Investigations. The outstanding feature of this outbreak was the effect of the new science of bacteriology in leading to the appointment of commissions of well-known workers to investigate the pathology of cholera on modern lines. During the height of the terrible epidemic in Egypt in the summer of 1883, Germany, France, and later America, sent some of their ablest men

to work in Egypt and subsequently in India, with the result that Professor Robert Koch discovered and isolated the comma bacillus of cholera. Unfortunately the English Government had refused in February 1883 to assist Dr. N. C. Macnamara I.M.S. in his desire to work at the subject, although his experience and writings on cholera were already well known and he had explicitly put forward the working theory that the rice-water stools of cholera contained some organism which was the cause of the disease—a view subsequently proved to be correct by Koch. After the publication of the German commission's report, the English Government sent an eminent bacteriologist to India to investigate Koch's conclusions, he reported against Koch's views and thus confirmed the Government of India in the negative attitude they had persisted in ever since the unfortunate Punjab inquiry of 1861. It is unnecessary to enter into this old controversy here, as Koch's findings are now universally accepted, although the work of D. D. Cunningham and others has shown that the organism varies more widely in its cultural characters than Koch originally allowed, and the agglutination test is necessary for the complete identification of the cholera bacillus. The proof at this time afforded of the specific nature of the infective agent in the stools of cholera patients, taken with the previous evidence accumulated by English sanitarians of food and water being the common vehicle of infection,

resulted in greatly increased accuracy and success of preventative measures, which have deprived epidemic cholera of much of its terrors as far as Europe and America are concerned. Unfortunately they are less applicable in the huge Indian endemic areas so densely populated by uneducated people.

1892–4. Epidemic in India, Afghanistan, Persia, and Europe. (Map VI)

1891 : 2. Severe at a large fair in the Purneah district of Bengal.
The great Kumbh fair at Hardwar passed off this year without cholera, as a result of excellent sanitary arrangements.

1892 : 3. Hardwar, at the annual fair, which was stopped, and the pilgrims dispersed.

,, 4. Kalka, Mian Mir, and Peshawar in the Punjab.

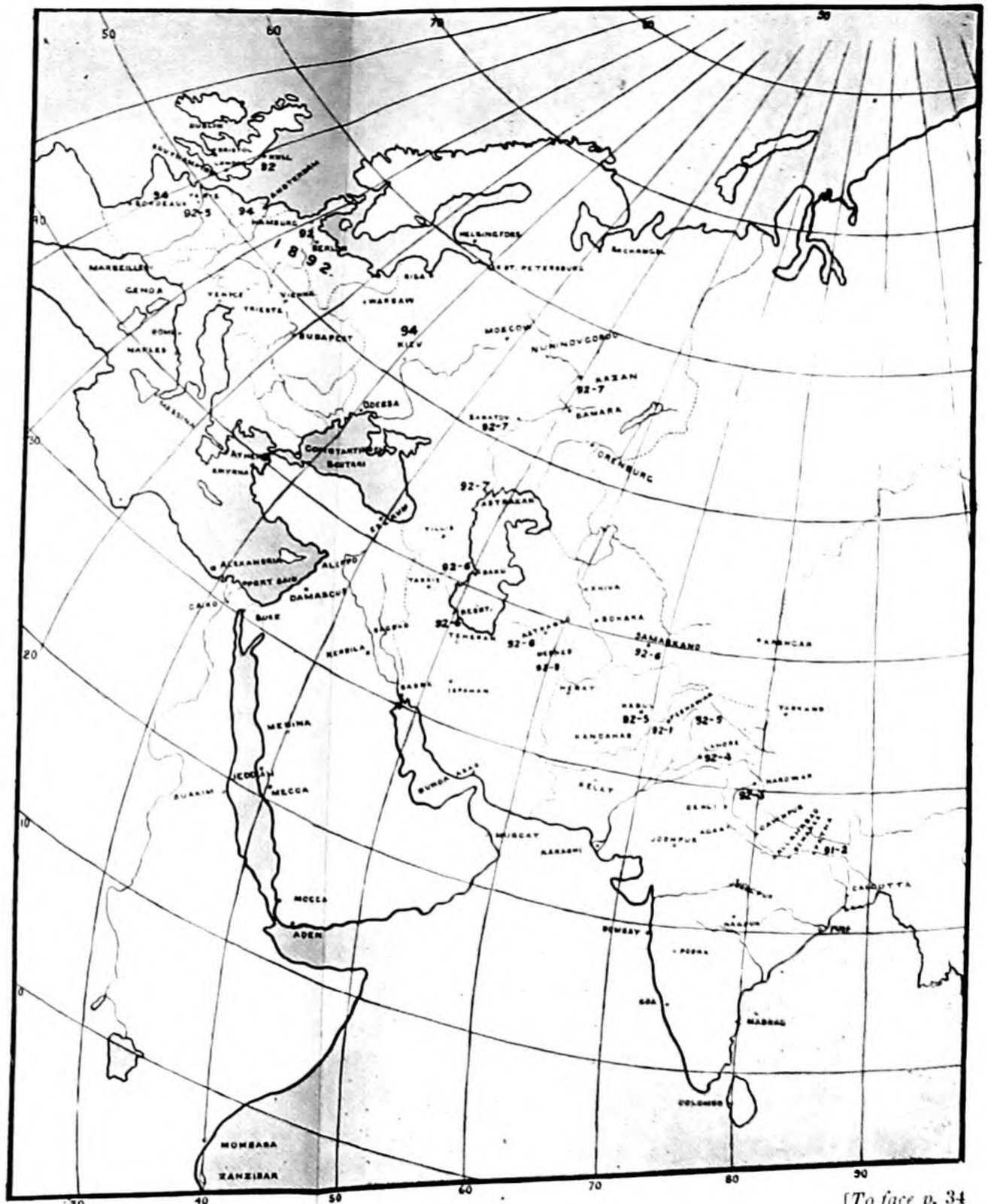
,, 5. Kabul very severely. Cashmir (5,000 deaths). Meshed in North-Eastern Persia, with 700 deaths daily. Also in Paris (? recurrence of 1885 outbreak).

,, 6. Astrabad, North Khorassan, Resht, and Baku on the Caspian Sea. Also from Taskend to Samarkand, the terminus of the Trans-Caspian railway.

1892 : 7. Astrakhan, and up the Volga to Saratoff, Kazan, and Simbursk.
In Northern Europe, especially at Hamburg. A few cases in English ports.

MAP VI, 1892–4

Epidemic in India, Afghanistan, Persia and Europe



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1893	Recurred in parts of Europe, including Hull, Grimsby, and Yarmouth.
1894	In West Russia, Galicia, Holland, and France, but died out by end of the year.

During this last outbreak, the English system of entirely giving up quarantine and trusting solely to isolation of the sick, following up and watching for some days all persons landing from infected vessels, was fully justified by the results, as no serious outbreak took place in Great Britain at this period, although numerous cases were imported from the Continent.

Cholera was severe in India during the famine years of 1897 and 1900. In 1902 it spread westwards to Arabia, Egypt, Syria, and Persia, and eastwards to Singapore, the East Indies, China, and Formosa, the Philippine Islands, and Japan. In 1903 Syria, Persia, and Asia Minor were attacked.

In 1904 cholera recurred in Southern Russia, spreading up the Volga from Astrakhan.

In 1905 it recurred in South Russia, and involved Egypt and parts of Germany, including Berlin and Hamburg.

In 1908 cholera was once more widely prevalent over India, and reached Russia in the autumn months, travelling as far as St. Petersburg. It recurred in Russia, and appeared in other parts of Europe to some extent in 1909 and 1910.

CHAPTER II

EPIDEMIOLOGY

Factors influencing the Origin and Spread of Cholera Epidemics

Endemic Areas of Cholera. Having dealt with the history of the principal great epidemic diffusions of cholera over the world, we may next consider their modes of origin and spread. As epidemic prevalence is but an extension from an endemic seat of the disease, we must first deal with the areas in which cholera is permanently located. Lower Bengal is the great home of cholera, from whence nearly all the great spreading epidemics have directly or indirectly arisen. In years in which cholera is not very widely diffused in India, a large majority of the total deaths from the disease in this country are returned from Bengal, while even in epidemic years more than half the total deaths occur in this province, as shown in Table I, of the annual deaths and ratios per thousand for each province during ten recent years. Madras and the United Provinces show the next highest figures, while the Bombay Presidency also reports a large number of deaths from cholera, although the yearly total varies more widely than in the former provinces. Lower Burma shows

TABLE I. YEARLY CHOLERA DEATHS AND RATIO PER 1,000 IN THE PROVINCES OF INDIA, 1898–1907

	Bengal.		*Madras.*		*Burma.*		*Bombay.*		*United Provinces.*		*Central Provinces.*		*Punjab.*		*All India.*	
	Total Deaths.	*Per mille.*	*Total Deaths.*	*Per mille.*	*Total Deaths.*	*Per mille.*	*Total Deaths.*	*Per mille.*	*Total Deaths.*	*Per mille.*	*Total Deaths.*	*Per mille.*	*Total Deaths.*	*Per mille.*	*Total Deaths.*	*Per mille.*
1898	76,169	·95	65,444	2·0	2,972	·66	4,378	·23	2,508	·05	7	—	33	—	152,703	·70
1899	116,058	1·43	29,082	·9	4,942	1·11	8,579	·46	8·579	·17	617	0·01	1,816	·09	171,410	·78
1900	369,639	3·70	60,662	1·8	3,440	·77	163,889	8·71	84,960	1·81	81,489	6·6	28,260	1·37	797,222	3·70
1901	118,221	1·48	81,370	2·2	3,552	·64	13,600	·74	53,995	1·13	66	·01	297	·01	271,210	1·21
1902	163,629	2·04	29,769	·8	1,844	·33	3,230	·17	25,160	·53	44	·01	371	·02	224,136	1·01
1903	211,765	2·64	27,393	·7	5,346	·97	1,825	·09	47,159	·99	437	·03	16,042	·71	312,854	1·37
1904	143,289	1·79	23,109	·6	2,472	·45	13,156	·71	6,617	·14	2,967	·24	717	·03	192,835	·85
1905	288,651	3·60	16,888	·5	3,511	·63	5,396	·29	121,790	2·55	1,217	·10	2,497	·11	441,786	1·96
1906	300,874	3·75	142,811	3·9	5,529	·99	46,119	2·50	149,549	3·14	38,768	3·26	4,232	·19	690,519	3·05
1907	282,883	3·52	81,565	2·2	7,964	1·13	7,656	·41	22,438	·47	4,291	·36	703	·03	408,102	1·81
Total	2,071,178	—	568,093	—	41,572	—	267,828	—	522,318	—	129,903	—	54,968	—	3,662,777	—
Average	207,118	2·59	56,809	1·6	4,157	·77	26,782	1·43	52,232	1·10	12,990	1·06	5,497	·24	366,278	1·64

a steady, although lower incidence. On the other hand, both the Punjab and the Central Provinces are practically free from the disease in some years, and only occasionally register many deaths from cholera. Indeed before the days of rapid railway communication throughout India, the Punjab and western portions of the North-West Provinces, as well as the Central Provinces, were frequently recorded to be entirely free from cholera, as repeatedly mentioned in the foregoing history, while after their invasion by epidemics the disease used to die out again very completely. They therefore scarcely belong to the true endemic areas of cholera, from which epidemics primarily arise, although their extensive infection from Lower Bengal is the usual prelude to an epidemic diffusion of the disease beyond the boundaries of Hindustan.

It will be observed that the endemic areas are all low-lying and largely alluvial tracts, while the elevated tablelands of the Central Provinces, the Punjab, and also the Chota Nagpur plateau of Bengal, are very much less affected by endemic cholera.

Apart from India cholera is endemic in parts of the West Indies, Java having suffered as far back as 1629. It also occurs yearly in Southern China and the Philippine Islands. To the west the disease is so frequently carried to Persia and Arabia that it is difficult to say if it has become endemic in those countries or not. From 1851 to 1861 it was certainly present every year in Persia, but appears

to have been frequently absent in subsequent years, so that it is probably not permanently located in that country. The same remark applies to parts of south-east Russia.

Extension of Epidemic Cholera from India along Trade Routes. The preceding chronological history is one long record of the spread of cholera from the endemic areas in India by means of human intercourse along the great trade highways by land and sea. The rate of travel was regulated by the rapidity or otherwise of communications between different places at varying times. The several epidemics have reached Europe by three different routes. Firstly, overland through the Punjab, Afghanistan, and Persia to Southern Russia, as illustrated by Maps I, V, and VI of the 1826–37, 1868–70, and 1892–3 epidemics respectively. That of 1841–9, shown in Map II, is also an exceptional variety of this route, in which the disease reached Afghanistan by the roundabout way of Chinese Turkestan from China, to which it had been taken by Indian troops from Calcutta. The succeeding outbreaks travelled to Europe in shorter times than the earlier ones owing to continuous increase of the rapidity of communications in each decade, so that in 1892 cholera travelled from India to Europe in as many months as the 1826–37 epidemic had taken years to cover the same route. In 1908 a similar rapid communication of cholera from India to St. Petersburg within a few months was again witnessed, so that these sudden European outbreaks

should now be looked for whenever the disease invades the countries to the west of the Punjab.

Secondly, we have the mixed sea and overland route from Western India to the ports of the Persian Gulf, and then up the Euphrates valley to Asia Minor and Southern Russia. This is illustrated by Map III of the 1848–53 epidemic, during which the Punjab, Afghanistan, and North-west Persia remained unaffected, although the disease appeared at the head of the Persian Gulf in 1851 and overran South Russia and Western Europe in 1853. The 1865 epidemic also partly traversed the Euphrates valley, although its main stream took the third route by sea from Bombay to Arabia, and was scattered broadcast by the agency of the Mecca pilgrims through Egypt and Syria to the Mediterranean ports of Southern Europe, as illustrated by Map IV. The spread of cholera was here again very rapid, the disease being carried from Bombay to the west coast of Arabia and Suez in May 1865, and to Marseilles and Paris in the next month of June, while by December it had reached New York. The same route was followed by the 1881–3 outburst, when Egypt and Southern Europe suffered so severely that permanent measures were taken to safeguard the vast Asiatic commerce, which had been diverted to this course by the opening of the Suez Canal in 1869.

The Spread of Cholera by Pilgrimages and Fairs. Numerous examples have already been recorded of great epidemics of cholera, both in India and

beyond, which have been associated with, or actually originated in, an outbreak at some greatly over-crowded and insanitary fair or pilgrimage, and been spread widely and rapidly by the dispersal of the gathering. The most important of these recurring festivals are at the Jaganath temple at Puri in the Orissa province of Bengal, Allahabad at the junction of the Ganges and Jumna rivers, and Hardwar at the debouchment of the Ganges from the Himalayas in the United Provinces. The dangers of the huge collections of people at the last two places, which vary from several hundred thousand in ordinary years to from one to three millions in every twelfth year, have for some time past been greatly lessened by the action of the Local Government in spending large sums on the sanitary organization of the camping grounds. These measures have been so successful that cholera is now frequently entirely absent and nearly always extremely limited in amount. Unfortunately the same cannot be said of Puri which is situated within the typically endemic area of the disease, here the sanitary arrangements have been largely left to the hands of a small and poor municipality, although upwards of 100,000 pilgrims often collect at the principal festival in July and about one-third of that number in the March fair. Endemic cholera is rarely absent from the district and outbreaks almost invariably occur at the time of these gatherings, which not infrequently assume epidemic proportions.

Thus in 1899 at the July festival 1,216 cases, with 1,020 deaths, took place in the town of Puri alone, great difficulty being experienced by the authorities in disposing even of the dead. From these annual outbreaks the disease is always spread over the district by the returning pilgrims, so that in the ten years ending 1899 (before railway communication was established with Calcutta) the cholera death-rate was three times as high in the Puri district as in any other district of Bengal, save the neighbouring one of Cuttack, which was also annually infected by the Puri pilgrims. The town of Cuttack used to yearly suffer severely from cholera until the pilgrims were made to travel round its outskirts without entering the city. Now that the railway carries the pilgrims in a few hours to Calcutta and rapidly disperses them over wide tracts of India, the efficient sanitary control of the Puri pilgrimages and especially the provision of a pure and thoroughly safe-guarded water supply, has become a matter of grave imperial concern. On the other hand, the local danger to Orissa has been considerably lessened by the cessation of the long marches of infected pilgrims through that area. A temporary increase of cholera, however, always occurs in Calcutta immediately after the Puri pilgrimages, being most marked when the disease is especially prevalent at Puri. The same remark applies to other fairs and pilgrimages in the neighbourhood of Calcutta, a considerable proportion of cholera cases

in Calcutta occurring among pilgrims returning through the city from various sacred places.

Beyond India the most important pilgrimages are those at Kerbela in the Euphrates valley, and above all at Mecca in Western Arabia, a number of examples of cholera at each having already been mentioned. Now that the Turkish railway has been carried south to Medina and will before long reach Mecca itself, bringing it into rapid railway communication with Asia Minor and Turkey, the great Mohammedan pilgrim centre will become a still greater source of danger to Europe, unless a much more efficient sanitary control is exercised in the near future by the suzerain Power.

Seasonal Incidence and its Relationship to Meteorological Conditions

In Lower Bengal, the home of cholera, the disease is present all the year round. Nevertheless, it shows very constant seasonal variations in the extent of its prevalence, which are illustrated by the monthly Calcutta mortality returns for ten years and the principal meteorological data as given by Wall in Table II, also by the monthly admissions to the Calcutta Medical College Hospital from 1895 to 1905 shown in Table VIII, p. 136.

It will be seen from these figures that a marked rise in the prevalence of cholera begins in Calcutta in February and lasts through the dry hot weather months of March to May. The numbers begin to fall again with the onset of the rains at about the

TABLE II. MONTHLY CHOLERA MORTALITY AND METEOROLOGICAL DATA IN CALCUTTA (WALL).

Month.	*Mortality ten years.*	*Average temperature.*	*Rainfall.*	*Subsoil water in feet.*
January .	1,955	67·7	0·44	13·8
February .	3,226	73·7	0·83	14·2
March . .	4,848	80·5	1·28	14·4
April . .	4,658	84·7	2·49	14·6
May . . .	3,396	86·2	5·46	14·7
June . . .	2,231	84·9	12·13	14·0
July . . .	1,318	83·5	12·64	12·2
August . .	1,684	83·1	13·71	9·6
September .	1,543	83·3	10·17	8·2
October .	1,805	81·5	5·61	9·7
November .	2,798	74·9	0·66	11·5
December .	2,175	68·1	0·24	12·9

middle of June, to reach the minimum during the wet monsoon months of July to September. After the cessation of the rains sometime in October a slight increase takes place from November to January which completes the yearly cycle.

The monthly **Variations in the Subsoil Water Levels** are shown in the last column of Table II, from which it appears that the hot weather maximum prevalence of cholera occurs with a low and stationary ground water, and the decrease to the minimum when the ground water is rising to its highest point ; being thus totally at variance with Pettenkoffer's theory.

The **Mean Temperature** in Calcutta is never low enough to have any marked effect on the prevalence of cholera, but a winter decline of the disease is

a very marked feature in the colder north-western parts of India as well as in Europe during epidemic prevalence.

Seasonal Incidence of Cholera in Different Provinces of India

The variations in climate in different parts of India afford excellent data for studying the effects of meteorological conditions on the seasonal prevalence of cholera. Table III has been constructed to illustrate as concisely as possible the most important points brought out by such an inquiry. Bellew, in his *History of Cholera in India from* 1862 *to* 1881, gives the monthly deaths from the disease in each province year by year. The averages of these yearly figures are entered in Table III, together with the monthly rainfalls for the same period and the mean monthly temperatures for several years. Thus the most important climatic factors can be readily compared month by month with the cholera prevalence in different provinces—the salient features are briefly as follows.

In **Bengal** (including Eastern Bengal) as well as in **Assam**, the seasonal incidence closely follows that of Calcutta which has been already dealt with. The decline in the early part of the rainy season is, however, less marked on account of the uneven onset of the monsoon in this immense area. The high rate in January was due to an extraordinary outbreak in one year, when over half of the ten years' mortality dealt with occurred.

TABLE III. MONTHLY PROVINCIAL CHOLERA DEATH-RATES, RAINFALL, AND MEAN TEMPERATURES, 1862–81.

	Bengal.		*Assam.*	*United Provinces.*			*Punjab.*			*Central Provinces.*			*Bombay.*		*Madras.*					
	Deaths.	*Temperature.*	*Deaths.*	*Deaths.*	*Temperature.*	*Rainfall.*	*Deaths.*	*Temperature.*	*Rainfall.*	*Deaths.*	*Temperature.*	*Rainfall.*	*Deaths.*	*Rainfall.*	*Deaths.*	*Temperature.*	*Rainfall.*	*Deaths.*	*Temperature.*	*Rainfall.*
January .	71,449	66·2	5,089	2,537	60·4	·74	743	54·9	1·01	25	69·7	·47	531	·18	7,485	76·1	·43	2,883	76·6	·08
February .	40,549	71·2	3,371	2,852	64·9	·75	514	53·1	1·36	52	74·7	·42	607	·09	5,571	77·4	·29	2,666	79·2	·20
March . .	55,589	80·2	5,224	18,365	75·9	·63	705	64·6	1·45	175	78·9	·54	1,091	·12	4,464	81·1	·48	3,308	83·9	·42
April . .	93,635	85·7	11,221	96,224	86·7	·32	7,570	81·2	·99	589	90·9	·47	2,176	·26	3,821	85·2	1·29	3,615	87·4	2·10
May . .	74,605	86·0	13,752	97,675	91·4	·89	19,475	89·1	1·02	2,147	95·6	·82	3,958	·65	4,497	89·8	3·01	2,649	84·6	11·35
June . .	65,562	84·8	13,076	92,810	90·9	4·22	18,288	93·3	2·38	3,415	88·4	8·04	4,829	8·64	5,224	89·6	6·22	2,790	80·1	27·19
July . .	59,486	83·3	9,148	65,566	85·8	12·12	15,883	90·0	7·91	2,821	81·6	14·67	4,117	11·80	7,491	87·2	6·92	5,203	80·6	31·38
August .	47,489	82·7	4,296	83,397	84·5	10·21	21,038	88·0	6·61	2,285	80·8	11·79	3,206	8·77	7,579	85·5	6·51	4,640	80·4	27·57
September	23,875	82·8	2,884	57,433	83·4	6·68	16,870	85·8	2·88	935	81·6	8·26	1,485	5·92	5,834	85·0	5·87	2,283	80·8	18·77
October .	19,099	80·5	4,267	48,927	78·4	1·19	7,664	77·1	·49	231	79·3	1·69	997	1·98	3,283	82·1	7·06	2,213	81·8	9·22
November	37,615	73·0	7,324	25,840	68·1	·04	1,558	65·3	·23	142	72·7	·26	481	·38	3,344	78·7	4·62	2,643	80·0	2·40
December	65,660	66·3	8,562	11,245	61·0	·25	577	56·8	·76	247	67·8	·21	366	·14	5,403	76·5	1·64	3,166	77·3	·17
Total Average	654,663	—	94,837	621,097	—	—	110,930	—	—	13,521	—	—	23,854	—	63,424	—	—	38,049	—	—
Average .	58,555	—	8,903	51,758	—	—	9,244	—	—	1,127	—	—	1,988	—	5,285	—	—	3,171	—	—
Rate per mille	1·87	—	2·24	1·40	—	—	0·35	—	—	2·23	—	—	1·67	—	2·37	—	—	1·36	—	—
Average Rainfall	65·33	—	137·25	—	—	38·16	—	—	27·37	—	—	47·78	—	—	44·58	—	—	130·89	—	—

In the **United Provinces of Agra and Oude** (formerly known as the North-West Provinces), a similar maximum occurs in the hot season to that in Bengal, only the main rise begins somewhat later, namely in March, on account of the longer cold season in the Upper Province. The decline is also somewhat less marked during the monsoon months, as the rains are less heavy and sustained than in Lower Bengal. Further, there is a marked decline in December and a very low minimum in January and February, in accordance with the greater degree of cold in those months than in Bengal.

The **Punjab** shows a still further accentuation of the above differences between the seasonal prevalence of cholera in the United Provinces and that in Bengal. Thus owing to the prolonged cold-weather season the hot-weather rise begins still later, being slight in April and becoming very marked only in May. On the other hand, the maximum prevalence extends through the rainy months of July to September with unabated vigour, owing to the monsoon current bringing but scanty rain as far inland as the Punjab. The decline commences with the fall of temperature in October, and reaches a well-marked minimum in the very cold season from December to March, during which the cases average under one-thirtieth of that of the maximum months, instead of about one-third as in Bengal with its far more equable temperature. The effect of increasing cold is thus clearly seen, and is in accordance with the almost complete

disappearance of epidemic cholera from Europe during the winter months, except sometimes in Russia, where the houses are kept very warm by artificial means.

Bombay City and the **Bombay Presidency** show different types of seasonal distribution. The island on which the city of Bombay is built is situated only just above sea level and cholera here has a similar season to that in Calcutta, namely a maximum in the hot dry months and a minimum in the wet monsoon ones. January and February, however, show a less marked minimum in Bombay in accordance with the higher temperatures in those months than in Calcutta. The Bombay Presidency, on the other hand, includes but a narrow strip of low-lying coast land, the greater bulk of the area being situated at a higher but variable elevation above sea level as it includes the Western Ghats and part of the plateau to the east of that range. These higher areas have a good cold-weather period with a very low cholera incidence. The annual rise is not marked until April and May and extends through the rainy months of June to August, declining again in September and October to reach a minimum in the cold months of November and December.

The **Central Provinces** consist of an eastern extension of the central plateau inside the Western Ghats and show a similar distribution of cholera to that of the Bombay Presidency just described. The winter seasonal minimum prevalence is still

more accentuated on account of the uniformly marked cold weather in this area, while the rise in the hot weather only becomes well marked in May and continues to August. Thus we see that in all the elevated parts of India the hot-weather rise continues throughout the rainy season, this may be explained by the districts having a comparatively low ground-water level so that they are not usually flooded and their tanks and wells thoroughly flushed out during the monsoon months, as in the case of rice-growing Lower Bengal and to a less extent in the alluvial plains of the United Provinces.

Madras, with its very equable climate and absence of any marked cold season, except in the elevated but more sparsely populated central portion, shows a more uniform monthly incidence of cholera than any other province of India. The more extensive and thickly populated eastern portion of the presidency is not within the area which feels the full effects of the south-west monsoon and the main rainy season here occurs during the north-west monsoon from October to December, which is also the minimum cholera season. Only isolated rain-storms take place from June to August and the maximum cholera season occurs in these hot months, the next highest rate being in the comparatively warm dry season from December to February.

In **Lower Burma** the distribution of cholera is also very uniform throughout the year, in accord-

ance with the warm equable nature of the climate. The maximum, which is not very much elevated above the average in the years dealt with in Table III, occurred in the very wet months of July and August, but this was due to very high rates in these months in certain years for as a rule the maximum rise takes place in the hot-weather months from March to May, as in other similar warm alluvial low-lying areas of Bengal.

Cycles of Cholera Years. Bellew in his elaborate statistical study of cholera laid great stress on a marked tendency for the disease to be unusually prevalent every third year, this being followed by a year of moderate number of cases and this in turn by a great diminution, or in some parts even an almost complete absence of the disease. Of the six three-year periods he dealt with, in four this sequence of events was more or less well marked, while he explained the two remaining exceptional triennial periods as due to abnormal excess of cholera in certain famine years. A. Herbert, I.M.S., published in 1894 (*Indian Medical Gazette*) some studies of the relationship of cholera to meteorological conditions in the more southernly provinces of India. In Bombay he traced a marked relationship between abnormally high atmospheric pressure in the hot weather, which in turn is dependent on deficient rain, and unusual prevalence of cholera. In Madras excess of cholera was related to a deficiency of the south-west monsoon, which also meant but little rain in the hottest time

of the year. In Berar, including the neighbouring eastern districts of the Bombay Presidency, he found most cholera in years of excessive rainfall, the black cotton soil of these parts being so absorbent that it is only in such years that there is sufficient surface-water to allow of the free development of the disease. Deficient rain in the low-lying water-logged deltaic and alluvial areas leads to stagnant and polluted water-supplies, which are flushed out in the rainy season with an immediate fall in cholera, so that in either case the distribution is explainable on the water-borne theory.

Herbert also lays stress on a cyclical distribution of cholera in Berar. I have studied the figures for nearly thirty years since the period dealt with by Bellew and although his three-year cycle is very far from being constant there is still a marked tendency for excessive prevalence to occur every few years and to follow on one or two years of very low cholera rates. This tendency is most marked in the more elevated provinces of Central India and the Punjab, although not always reaching a maximum in the same year in each province, it is accompanied by a slighter excess in the low-lying more strictly endemic areas.

This cyclical distribution of cholera points to the more serious outbreaks in some degree exhausting the supply of susceptible people and so producing for a time a population unfavourable for its active propagation. After two or more years of low

prevalence this relative immunity wears itself out, and given suitable meteorological conditions a severe outbreak once more occurs. As Herbert points out, in Berar excessive rain has little effect in producing a serious outbreak of cholera if one has taken place in the preceding year, although after one or more years of low incidence an excessive monsoon always causes a great excess of cholera. The influence of periodicity in the occurrence of severe cholera outbreaks thus appears to be an important fact, which must be taken into account in addition to meteorological conditions in studying the epidemiology of the disease. As already shown, these conditions vary so much in different parts of India that each province presents a separate problem and no general hard-and-fast rule can be laid down regarding the factors influencing the yearly prevalence of cholera in India as a whole.

CHAPTER III

ETIOLOGY AND PROPHYLAXIS

Discovery of the Comma Bacillus of Koch. The earlier speculations regarding the etiology of cholera have already been dealt with in the historical section of this work. Our real knowledge of the causative agent of the disease dates from Koch's discovery of the comma bacillus at the time of the Egyptian outbreak in 1883. His great authority led to his conclusions being very generally accepted within a short period, although there were not wanting those who denied the truth of many of his contentions. Further studies soon revealed other comma-shaped bacilli with cultural characters closely resembling in many respects Koch's original cholera organism, such as Deneke's bacillus found in cheese and Finckler and Prior's spirillum, although these had little pathogenic properties and did not agglutinate with cholera serum.

D. D. Cunningham's Researches. At a later date the careful and prolonged researches of Professor D. D. Cunningham, I.M.S., in Calcutta (*Scientific Memoirs of Indian Army Medical Officers* 1885 *to* 1895) conclusively proved that the comma bacilli of cholera differed widely from one another in mor-

phology and cultural characters and were very far from being a single clearly defined form as originally described by Koch. The importance of these observations was borne out at the commencement of the Hamburg cholera outbreak in 1892, when a number of cases occurred before an organism giving the typical characters of Koch's first described comma bacillus was isolated and the occurrence of Asiatic cholera officially admitted. Much confusion has arisen owing to differences of opinion among eminent bacteriologists working in different laboratories, as to whether certain strains of comma bacilli were the true organisms of cholera or not, and researches carried out with one species by certain workers were denied any validity by others who used comma bacilli of a different origin. The Vibrio Metchnikovi, the Nasik and the El Tor commas, are instances in point.

Pfeiffer's Agglutination Test. Fortunately the subject has been largely rescued from a very complicated and confused position by Pfeiffer's great discovery of the phenomenon of agglutination. This was first observed by him after the injection of comma bacilli into the peritoneal cavities of guinea-pigs, but it was subsequently simplified by being found to be equally marked on mixing *in vitro* the organism and the serum of a highly immunized animal. Kolle and Wassermann's extensive observations have shown that the various comma bacilli of cholera agglutinate in very high dilutions,

while harmless saprophytic water comma organisms fail to do so and can be thus readily differentiated. This I have confirmed in a number of observations carried out during the last few years in Calcutta, and at the present time it is by far the most reliable method of recognizing the specific organism of Asiatic cholera. By subcutaneously inoculating a rabbit three or four times at weekly intervals, beginning with minimal lethal doses, a serum with strong agglutinating properties can readily be obtained. It can also be purchased in dried form from European laboratories and it keeps well, so that a little may be dissolved whenever wanted. Such a serum obtained from the Vienna Bacteriological Institute clumps cholera commas as a rule up to dilutions of 1 in 10,000 or more and so is quite reliable. The macroscopic test is the most convenient one for this purpose.

Recognition and Isolation of the Comma Bacillus in Cholera Stools. It was Koch who first showed that cholera stools as a rule contain vast numbers of lightly staining comma-shaped bacilli, which may be so numerous as to constitute almost the only organism present and even yield a pure culture by direct inoculation on agar. Klein, Cunningham, and others denied that there is any relationship between the number of comma bacilli present in the stools and the severity of the disease. They held that these organisms are normal inhabitants of the intestinal tract, which find in the altered state of the bowel contents in cholera very

favourable conditions for multiplication and thus bear only an accidental and not a causative relationship to the disease. It is quite true that there is not an absolutely constant proportion between the severity of cholera and the number of comma bacilli in the evacuations, especially if no account is taken of the stage of the affection. Microscopical examinations of a large number of stools in the acute evacuation stage of cholera cases in Calcutta, have, however, convinced me that as a general rule such a relationship does to a considerable extent hold good. This is especially marked in the most severe cases, in which I have frequently found the stools to consist of nearly a pure culture of comma bacilli, which could be readily isolated by direct inoculation of a suitable solid medium. These cases are very liable to prove rapidly fatal in spite of active measures which are successful in a great majority of cholera attacks, thus displaying a very exceptional degree of virulence. On the other hand, in mild cases the comma bacilli are much less numerous in the evacuations and require special measures for their isolation. Moreover, the toxicity of different strains of cholera comma bacilli differs considerably and this may easily account for occasional variations in the numbers of the organisms irrespective of the severity of the case, without even taking into account the susceptibility of the patients to the disease.

When the characteristic rice-watery stools of the acute stage are obtainable, there is no difficulty

in finding numerous comma bacilli in them or in isolating the organism in pure culture. One of the white mucous flakes, which separate from the clear fluid on standing and settle to the bottom of the vessel, is smeared with a platinum loop on a slide and stained for a short time with either carbol fuchsin freshly diluted with several parts of water or with gentian violet. The coli bacilli and other organisms of normal fæces stain darkly, while the curved comma-shaped organisms are rather lighter in tint and some of them are often united by their ends into spirilla-like chains. They vary considerably in length and thickness in different cases, from short, thick, slightly curved rods to long, thin ones, while the degree of curvature is also variable. Figure 7 shows some of the types which may be commonly met with, it is taken from Professor D. D. Cunningham's paper on 'The results of continued study of various comma bacilli occurring in Calcutta', published in the *Scientific Memoirs* in 1893. No. 1 depicts a fairly typical appearance in pure culture, including some long spirilla-like forms. No. 2 shows a short, thick variety, and No. 3 a longer and thinner one.

When the comma bacilli are extremely numerous several agar slopes or plates may be inoculated directly from the stools, but in all cases, in addition, one or two flasks containing 100 c.c. or more of peptone water (2 per cent peptone and 1 per cent sodium chloride) are used and incubated at blood heat for from eight to twenty hours. In this

medium the comma bacilli multiply more quickly than the normal intestinal flora and tend to collect on the surface of the fluid, where they may form a thin pellicle from which sub-cultures may readily be made on agar. If they are still not very numerous, a second and even a third sub-inoculation into peptone water may be required before a sufficient preponderance of comma bacilli is obtained to allow of their isolation. Usually, however, a few hours suffices for their easy demonstration in large numbers. I have also found Dieudonné's medium of considerable help when the comma bacilli are scanty as it allows of their ready growth while inhibiting that of coli bacilli.

Morphology and Cultural Characters. Attention has already been called to the considerable variations in the morphology of cholera bacilli. They are motile, as they possess a single terminal flagellum, but not very actively so. On prolonged culture they may alter considerably in appearance apart from degenerative changes. Thus, Metchnikoff succeeded in permanently altering the short and curved bacilli into long and nearly straight ones by cultivation under special conditions; thus showing that they are pleomorphic and cannot be separated into distinct species by their morphological characters as Cunningham originally held.

Closely parallel variations are also found in their cultural characters in certain media. This is best seen in the different degrees of liquefaction of the same batch of gelatine tubes by diverse strains of

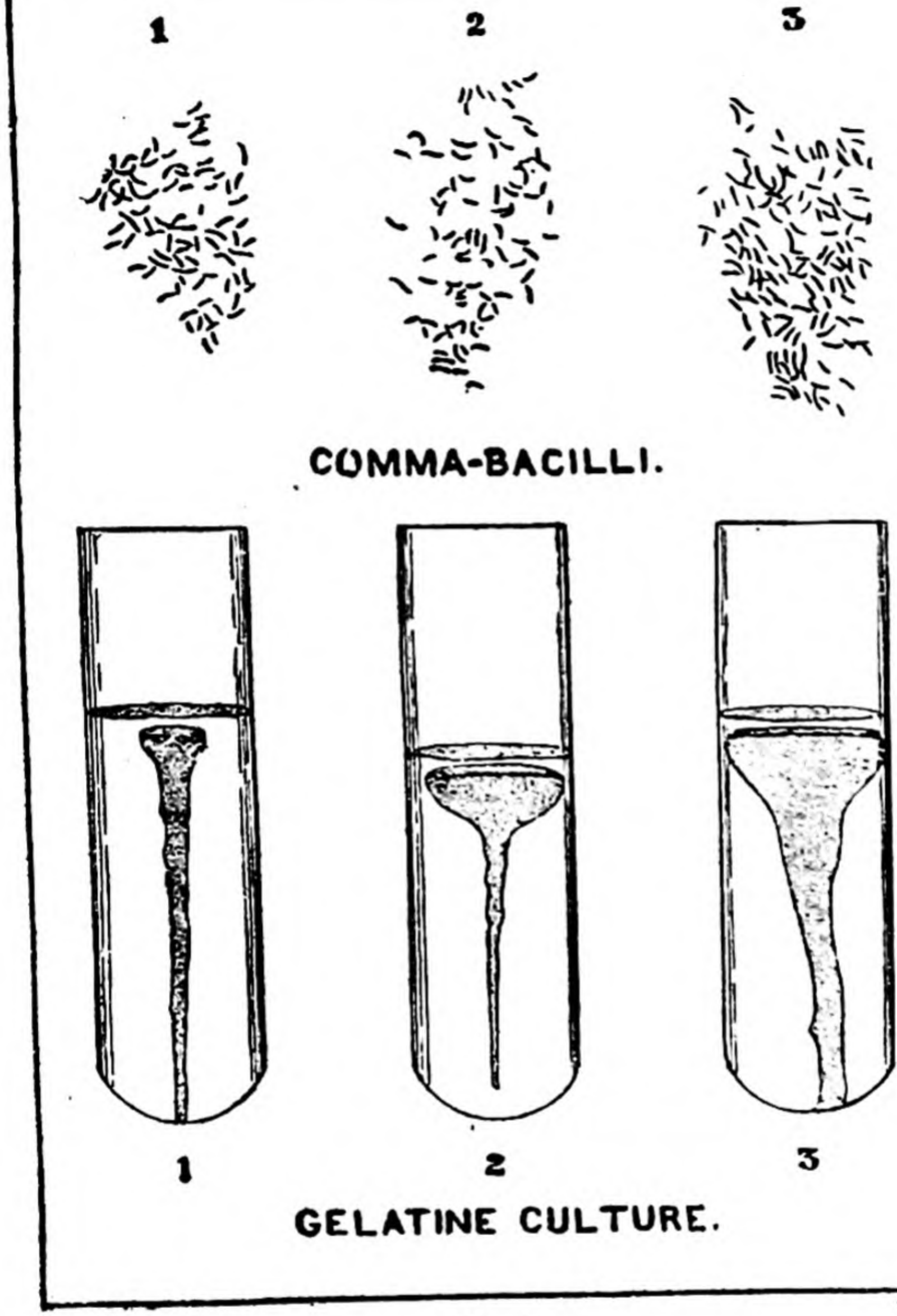


FIG. 7.

Forms and cultural characteristics of Cholera bacilli.

Bacilli: 1. Typical pure culture. 2. Short thick variety. 3. Long thin variety.

Culture results of varying amounts of liquefaction in gelatine culture.

cholera commas. The typical appearance produced in this medium is a slow liquefaction which takes place most rapidly at the upper part of the tube in contact with the air and much more slowly in the deeper portions. In this way a turnip- or funnel-shaped softening of the gelatine is produced, as shown in the drawings in Figure 7, which are taken from D. D. Cunningham's paper already referred to and well illustrate the variations from a slight superficial globule to an extensive liquefaction throughout the whole length of the inoculation stab. This property may also vary considerably after long cultivation from the original power of the strain, while similar appearances are produced by non-choleraic vibrios, so that these appearances in gelatine cultures will not suffice for the identification of the pathogenic organisms.

In **Gelatine** plates at 22° Cent. cholera commas at the end of twenty-four hours form small refractile colonies with an undulating border. This becomes more marked with further growth, while the surface becomes refractile and slightly depressed. As liquefaction proceeds the colonies sink into the medium and these characters are lost. Here again the typical appearances are by no means constant and they tend to become altered in strains kept long under laboratory conditions. Such colonies are not, however, found in abundance in plates made from normal fæces, so they are of service in separating pure cultures of the organism although in the tropics the use of gelatine is commonly

rendered troublesome by the high temperature prevailing.

In **Broth** cholera commas produce a hazy appearance and may form a thin pellicle on the surface of the fluid, while later a flocculent precipitate is seen on the bottom of the tube.

On **Agar** slopes the organism forms semi-transparent yellowish streaks with a slightly undulating border, somewhat opalescent by transmitted light. On agar plates they may be distinguished by their thin transparent appearance from coli bacilli.

On **Potato** at blood heat this bacillus may present extremely variable appearances, some strains growing with difficulty and others very readily. The usual character is a semi-transparent dirty-white or yellowish-white film, but occasionally a marked formation of pigment takes place and the colour may vary from yellow through orange to a darkish-red tint. These are well illustrated in D. D. Cunningham's paper in the *Scientific Memoirs of* 1891, I have confirmed his observations and obtained potato cultures showing quite as marked colour variations as he depicts. Such occasional variations probably have no more pathological significance than the differences in colour of staphylococci.

The Indol Reaction. When grown in peptone broth containing a small amount of nitrate (which is usually present in broth) the nitrate is reduced to nitrite and indol is produced at the same time. If after about three days half a c.c. of strong

sulphuric acid is added a red reaction is produced as in the case of coli bacilli. Although this reaction may occasionally be produced by other vibrios, yet its absence is said to be of some importance in excluding the cholera organism, provided nitrites are known to be present at the time the test is made. A more delicate way of performing it is to add an acid solution of dimethyl-amido-benzaldehyde and a watery solution of potassium persulphate, which give a cherry-red colour.

I have found that the rice-water stools of cholera give a marked indol reaction with the last-mentioned reagent, but there was no definite relationship between the degree of reaction and the severity of the disease. This fact militates against the recent suggestion of Emmerich that the symptoms of cholera are due to the absorption of nitrites from the bowel: a theory which fails to account for many other facts regarding cholera toxins and their antitoxins.

In **Milk** the cholera bacillus grows well for a time without producing any visible change, but it rapidly decreases in numbers if acid fermentation sets in, so that fresh milk into which the organism may have gained access, usually through dilution with contaminated water, is an important source of infection. A few years ago a very experienced medical man, overcome by thirst, drank a glass of milk procured in a native bazaar and was attacked by cholera during the following night with a fatal result.

Hæmolytic Reaction. Another test consists of smearing a layer of blood over the surface of an agar plate and inoculating a streak of a cholera culture across it. After a day or two a transparent appearance will be produced around the line of growth and extending well beyond it, owing to hæmolysis having been produced by the action of the chemical products of the bacilli. So far I have only obtained this reaction with cholera vibrios giving the serum reaction in high dilutions, but have not yet had sufficient experience with non-pathogenic commas to allow of any dogmatic statement as to the exact diagnostic value of the test.

The Resisting Powers of the Cholera Bacillus. The most important fact influencing the powers of the comma bacilli to live outside the human body is their feeble resistance to desiccation, which in a few hours will destroy their vitality if they are spread in a thin layer. On the other hand, if kept moist, as in soiled clothes under conditions which prevent complete drying, the organism may retain its vitality for a long period. Instances are on record of the infection having been conveyed long distances by linen soiled with cholera stools and leading to outbreaks among those who have subsequently handled the clothes. They are quickly killed by heating to a temperature of from 56° C. for one hour or to 60° C. for ten minutes, but can resist cold of several degrees below the freezing point for some days. On the surfaces of fruit and vegetables they may live for several days in a cool,

moist place. They die out of sterile water in a short time, but in natural waters they may live for many days or even for months; some waters, however, appear to be harmful to them, including, according to Hankin, the Jumna water at Agra. The Hoogly water at Calcutta, however, certainly frequently contains them and the supply of filtered water to the ships on the river has greatly reduced the prevalence of cholera among the sailors.

Acids are very unfavourable to the cholera commas, from 0·02 to 0·05 per cent hydrochloric acid destroying them within a few minutes, especially in the presence of pepsin. If albumens are also present from 0·1 to 0·2 per cent of acid is required for the same purpose. The gastric juice thus affords powerful protection against the passage of the cholera bacillus through the stomach if the organ is in a healthy condition and this is doubtless an important factor in determining the capriciousness of the incidence of the disease among a population exposed to infection.

When a water has to be examined for cholera organisms; take 500 c.c. or more and add sufficient peptone salt solution, containing 20 per cent of peptone and 10 per cent of common salt, to make the mixture contain a one per cent solution of peptone. After eight to twelve hours make plates from the surface of the solution, in these any cholera organisms present will have greatly multiplied within the time and they can now be easily detected.

Duration of the Specific Cholera Bacillus in the Stools after Attacks of Cholera. As a rule the cholera commas cannot be found in the stools of patients a few days after the attack is over. Still they have been isolated from convalescents at from eight to fifty days after the symptoms had ceased. Moreover, during a cholera outbreak the specific organisms have been repeatedly isolated from the stools of healthy persons who have been in contact with cholera patients, who may thus form sources of further spread of the disease.

Cholera Carriers. During the last few years much attention has been directed to the possibility of healthy persons carrying the infection of cholera much in the same way as typhoid carriers have been so abundantly proved to do. In 1905 F. Gotschlich isolated vibrios 37 times from 107 post-mortems on pilgrims who had died of other diseases, there having been no cholera that year at the El Tor camp. Six of them agglutinated up to at least 1 in 500 dilutions with cholera serum. R. Pfeiffer in 1909 discussed this question, and expressed great doubt as to Gotschlich's El Tor vibrios being true cholera organisms. He found the stools of cholera patients usually free from infection within ten days, and never met with any chronic carrier. The absence of infection of the gall bladder and bile-ducts by the comma bacillus places the disease in quite a different position from that of typhoid in this respect. In Manila, however, carriers have been detected in a jail, where

unattacked persons were found to harbour the specific organism in their intestines. At present this appears to be a very rare event, but further investigation is required before the true rôle of so-called cholera carriers can be decided.

Degeneration of Cholera Bacilli in Artificial and in Natural Conditions. Another remarkable fact is the rapidity with which the great majority of cholera bacilli degenerate and die on ordinary culture media. Thus Gotschlich and Weitgung showed that in agar cultures after sixty-eight hours only 0·8 per cent of the organisms present at the end of twenty-four hours' growth still survived. They rapidly become very short or even coccal in shape and then lose their vitality. It is doubtless owing to this property that the infection so quickly dies out of the bowels of those who survive the disease.

In a similar manner the decline of epidemic cholera on the approach of cold weather also appears to be due to the degeneration and death of the bacilli when external conditions become less favourable to their multiplication outside the human body. Mr. Hankin of Agra published in 1895 a large number of observations made during the serious epidemic of cholera in the United Provinces in 1894. He made bacteriological examinations of the water supplies in a number of infected towns both during the outbreak and at intervals afterwards. At the earlier period comma bacilli were very frequently found in the wells, especially

those in close relationship with the disease. After one to three months of the cessation of the cholera, comma bacilli were only exceptionally found in the same wells, and those isolated had lost their virulence, either entirely or to a very marked extent as compared with those obtained from the same source during the height of the outbreak (*Indian Medical Gazette*, March, 1895, p. 92). The later observations were mainly made in November and December, when the cold season had set in, which thus coincided with the diminution in numbers and virulence of the cholera organisms and sufficed in Mr. Hankin's opinion to account for the winter decline of the epidemic. These observations were made before the introduction of the agglutination test for the identification of true cholera commas from the numerous non-pathogenic water ones, but they are nevertheless highly suggestive and worthy of repetition with the present methods of control. Professor W. J. Simpson and Mr. Haffkine (*Indian Medical Gazette*, 1895) made a very similar research regarding the prevalence of comma bacilli in Calcutta tanks, and found these organisms much more frequently in waters in whose neighbourhood cholera cases had occurred. D. D. Cunningham's observation that comma bacilli can be readily recovered from the intestines of fish must here be borne in mind, as the same objection regarding the absence of control by the agglutination reaction in high dilutions applies to their work, which therefore requires confirmation, when sufficient investigators

are available for the purpose in the home of cholera.

Pathogenic Properties of the Cholera Bacillus. Koch experienced great difficulty in establishing the specific nature of his cholera bacillus owing to animals not being readily susceptible to the disease. By neutralizing the acid in the stomachs of guinea-pigs and paralysing the intestinal movements with opium before administering cultures by the mouth he produced fatal results and recovered the bacillus from the intestines. Metchnikoff succeeded in infecting young suckling rabbits as long as they were living solely on their mother's milk and also showed that certain intestinal bacilli are inimical to the development of the organism of cholera. Rabbits have since been infected by intravenous injections of small quantities of cholera bacilli and may be killed in this way with congestive lesions of the intestines. Intraperitoneal injections of guinea-pigs also produce a fatal infection and afford a useful test of the pathogenicity of cultures. By repeated passages in these animals the virulence of a strain may be exalted. The Spermophilus gutatus, a Russian rodent, has been fatally infected with cholera, either by the mouth or intraperitoneally.

Even man shows only a partial susceptibility to the cholera organism. Metchnikoff carried out a number of experiments on the ingestion of cholera cultures by human subjects, and although more or less marked diarrhoea containing comma bacilli

was commonly produced, yet in only one instance did typical rice-water stools appear, although spontaneous recovery occurred without any treatment. His strains had probably lost much of their virulence during culture in the laboratory. On the other hand, a medical man working with cholera bacilli in a German laboratory developed a typically severe and ultimately fatal attack of the disease, and his stools contained almost a pure culture of the organism. As he had sucked up a portion of a culture into his mouth and there was no other case of cholera in the town at the time, this accident afforded very conclusive evidence of the pathogenicity of the bacillus. Healthy human beings present considerable resisting powers to infection by even virulent cholera bacilli, for when a number of persons consume the same infected food or water only a small proportion usually contract the disease. For example,—in Macnamara's well-known case, out of nineteen people who were known to have drunk some water which had recently been contaminated by a fresh rice-water cholera stool, only five developed the disease. This fact, together with the great variability in the virulence of the organism, go far to explain the apparent capriciousness of attacks during the prevalence of cholera.

Toxins and Antitoxins. The toxins produced by the cholera bacillus have been extensively studied with somewhat varying results. In 1893 Metchnikoff, Roux, and Salimbeni (*Annals d'Institut Pasteur*) produced fatal results in guinea-

pigs by placing cholera spirilla in collodion sacs in their peritoneal cavities and they attributed the effects to the formation of soluble toxins. Their conclusions, however, are open to doubt, as intracellular toxins may have been set free in the death and disintegration of the bacilli. McFadyean (*Lancet*, vol. ii, 1906), working at the Lister Institute, extracted intracellular toxins from cholera bacilli by freezing them with liquid air and grinding them up, he also produced active antitoxins in animals repeatedly inoculated with his toxins. In 1906 Brau and Dernier cultivated a Saigong cholera vibrio on horse serum and defibrinated blood, and obtained both a soluble toxin and also a more active intracellular one by maceration of the organisms. They succeeded in producing a slightly antitoxic serum in animals injected with the toxins. In 1907 Kraus and Russ obtained powerful toxins, and produced antitoxins in horses and goats, which had both a protective and a curative action against the toxins in mice. In 1908, Salimbeni, at the Pasteur Institute, also produced an antitoxic cholera serum, which has been used with some degree of success in Russia. Krawkoff extracted a very toxic nucleo-proteid from cholera bacilli. J. Z. Schurupow, of Cronstadt (*Cent. f. Bakt.* t. 49, 1909), extracted toxins from the bacilli with a weak alkali, and obtained an antitoxic serum from horses injected with it, which has been used in Russia. There is now fairly general agreement that the

specific toxins of cholera are essentially intracellular in nature, but owing to the rapid death and degeneration of the bacilli in cultures, they become dissolved to some extent in the culture medium. The results of antitoxic serum in animals are promising. For their use in man, see p. 217.

Prophylactic Inoculation against Cholera

Although Koch only discovered the cholera bacillus in 1883, yet as early as 1885 Dr. J. Ferran demonstrated experimentally that guinea-pigs could be protected against lethal doses of the organism by subcutaneous injections of living comma bacilli. Moreover, during that and the following year 50,000 persons were vaccinated against the disease during a great outbreak in Spain. Dr. Ferran states that he used pure bouillon cultures of the cholera bacillus, originally derived from human sources, which had been found extremely toxic for guinea-pigs. Owing to the very deficient state of vital statistics in Spain at the time, several commissions from different European countries were unable to satisfy themselves regarding the protective value of Ferran's method, although later the discoverer published a book on the subject, containing some strikingly favourable figures. Unfavourable results were, however, reported in some instances, apparently due to deficient technique in the stress of high pressure pioneer-work during an epidemic, and the Spanish Government discontinued the inoculations. Although at that time it

may be open to question whether many lives were saved by the vaccine, yet, as Metchnikoff says in his work on immunity, the fundamental experiments of Ferran were subsequently confirmed by different workers, and the Spanish doctor must be regarded as the originator of inoculation of cultures of the comma bacillus as a prophylactic against cholera, which in its turn led to the adoption of plague and typhoid vaccines in the hands of Haffkine and Wright.

In 1888 Gamaleia succeeded in immunizing guinea-pigs and pigeons against fatal doses of cholera vibrios by injecting sterile virulent cultures and showed that if the bacilli are killed by heat, the local reaction is also lessened. He therefore advised the use of these sterile vaccines in the human subject.

In 1892 Haffkine published the researches which led him to adopt the following modifications of Ferran's method. He first obtained a very virulent strain of organisms by twenty to thirty passages through guinea-pigs intraperitoneally, by which time the growth had attained a fixed strength and he found that the protection afforded by subcutaneous injections varied with the virulence and the dose. An attenuated virus for the first dose was next obtained by cultivating in broth at 39° C. in a constantly ærated atmosphere. By inoculation of this weakened virus first, the exalted one could be safely given after a few days and it produced immunity to all methods of infection. After inoculating himself

and others in this way with the production of only slight fever and malaise, he proceeded to India in February 1893 to try his method in outbreaks of cholera. For the first injection 0·1 to 0·05 c.c. of a twenty-four hours' agar tube of the attenuated culture suspended in broth was injected subcutaneously, and after three to eight days a similar dose of the virulent culture was given. He used the living bacillus in nearly all his trials, as he considered that heat or antiseptics for sterilizing them diminished the effect. Occasionally he used 0·5 per cent carbolic acid for sterilizing agar cultures.

Between 1894 and 1897 Kolle made several valuable contributions to the subject. He first clearly demonstrated that the blood-serum of those vaccinated with living or dead cholera bacilli had a powerful bactericidal and agglutinating effect on cholera organisms and this property was not destroyed by heat or chloroform. He therefore advised a single injection of a vaccine containing 2 milligrammes of bacilli (one-twentieth of an agar tube) to which 0·5 per cent phenol had been added, but occasionally employed twice that dose.

Numerous minor modifications of the above methods have been advocated from time to time, including various complicated chemical processes for extracting the nucleo-proteids, &c., from the bacilli. The most noteworthy are those of the late Dr. Allan McFadyean, who ground up the bacilli after freezing them to extract the intra-

cellular toxins and Richard P. Strong, who studied the question in Wassermann's laboratory. He found that the natives in the Philippine Islands would not submit themselves to Haffkine's method of inoculation on account of the severe local and general reaction it produced. The same objection has also led to inoculations against cholera in India during recent years having been very little used, few, except those Europeans who may be exceptionally exposed to the disease, being willing to submit to anticholeraic inoculation.

Dr. Strong set himself to work to prepare a vaccine containing the substances which provoked the formation in the system of bactericidal and agglutinating properties, but was less toxic than Haffkine's prophylactic, using Kolle's methods for measuring the degree of immunity produced. As it is now nearly universally acknowledged that the true cholera toxins are intracellular in nature, it is essential to extract these from the bacilli. In agar cultures, after forty-eight hours a very large proportion of the organisms are already dead, whilst a proteolytic ferment is present, which acts on the toxins, and largely converts them into the less poisonous toxoids, which still retain the power of provoking immunity. Taking advantage of the fact that this ferment is not destroyed by temperatures which kill the bacilli themselves, Strong proceeded as follows. Large flat-sided Kolle's flasks filled with agar are sprayed with a twenty-four hour bouillon cholera culture, and incubated

at 37° C. for twenty hours. The surface growth suspended in sterile water is heated in a sterile flask for one to twenty-four hours at 60° C., and then incubated at 37° C. for two to five days, to allow time for the proteolytic ferment to act on the dead bacilli. It is finally filtered through a Reichel candle to remove the remains of the organisms and is now ready for use. Strong prefers not to add any antiseptic and found it retained its powers well in the ice-box for five months. Owing to the decline of cholera in the Philippine Islands he had not been able to test it extensively on the human subject, but it proved to have but very slight toxic effects, although its powers of increasing the protective substances in the blood of men was higher even than Kolle's vaccine. The severe reactions produced by Haffkine's prophylactic, which have so greatly prevented its extensive use in India, appear to have been successfully overcome by Strong, whose method is worthy of full trial in India and elsewhere.

Results of the use of Prophylactic Cholera Vaccines. The only vaccine which has been very extensively tested in practice in India is that of Haffkine, who spent several very laborious years in inoculating over 70,000 persons, scattered over Bengal and Assam, under considerable difficulties. The results, although somewhat variable, were on the whole distinctly, and often decidedly, favourable, and are generally accepted at the present day as proving that his vaccine has a con-

siderable effect in reducing the liability to the disease. On the other hand, those who are attacked after it suffer quite as severely as the inoculated, the death-rate not being reduced. The smaller doses he first used had largely lost their protective effect after a lapse of fourteen months, as in the case of the East Lancashire Regiment and in Calcutta. Later, Dr. Powell, in Assam, used treble doses, and subsequently reported very favourable results, extending over four years. These large doses, however, cause severe, and occasionally dangerous, effects. During the four or five days following the first dose the degree of protection afforded is also comparatively slight, but after that period it rapidly increases. In two outbreaks in Bengal jails, in which as nearly as possible half the inmates were inoculated, without any selection, the death-rates among the inoculated were only one-half and one-fourth the death-rates respectively among the uninoculated. In two years' observations in Calcutta reported by the health officer, the reduction in the mortality obtained by the treatment was a threefold one. Lastly, with the very strong doses used by Dr. Powell in Assam, the reduction in the deaths among the inoculated was reported as being nearly an eight-fold one.

The above results are very encouraging, and it is much to be regretted that the severity of the reaction after the dose of Haffkine's vaccine, which is required to produce lasting immunity, is so great as to have led to the nearly complete

abandonment of his method in India without anything better having been substituted for it. The disease, however, is too rare among Europeans to make it worth their while to go through the suffering produced by the treatment, while natives of India can rarely be induced to submit themselves to it except under very special conditions. Cholera in India is so intimately associated with religious pilgrimages and fairs, that a field might perhaps be found from prophylactic treatment in the outbreaks which so frequently occur among such collections of people, if the resulting inconveniences could be so far reduced as to remove the present dread of the little operation, as may very possibly be done by the use of Strong's modification.

Mode of Infection of Cholera

Through Food and Water. The fact that the subcutaneous injection of living virulent cholera bacilli produces only a variable degree of toxic symptoms, followed by some degree of immunity, excludes such a mode of natural infection. On the other hand, the whole of the evidence goes to show that the organism always gains access to the human body through ingested food and water. As Ernest Hart well expressed it: 'You can eat cholera and you can drink cholera, but you cannot catch it.' The immunity of sick attendants in a well regulated cholera ward is in accordance with this fact. A number of examples of water-borne cholera have already been given in the historical

section. In recent times the most striking one is the very severe infection of Hamburg in 1892, and the almost complete exemption of Altona, the former having a direct supply of impure river water, while that of the latter was passed through sand filters before being distributed. The two towns are contiguous, and one side of a street with Altona water escaped cholera, while the other side with Hamburg water had numerous cases of the disease. The great reduction of cholera in Calcutta and other large Indian towns immediately following the introduction of filtered water supplies is equally conclusive.

Food only serves to carry cholera when it has been contaminated with cholera germs in a moist state, and not subsequently sterilized before being swallowed. Thus milk, which when it has been handled by natives is always diluted with water, often of a foul description, is a fertile source of cholera infection, unless it has been boiled before use (as it always should be if it cannot be obtained from a reliable European firm in sterilized bottles). Raw vegetables in salads and uncooked fruits are also dangerous foods in tropical climates, especially in the cholera season.

Flies have been proved to be capable of conveying living cholera bacilli from evacuations into food supplies, and several outbreaks of cholera in India have recently been attributed with good reason to this mode of infection. Insanitary conditions, especially dung heaps, breed swarms of

flies, and so may be a factor in the spread of cholera and other fly-borne diseases. The immediate disinfection of the evacuations of cholera patients will materially limit the chances of infection.

Infection by **Soiled Clothes** has already been referred to as having been responsible for various outbreaks of cholera, and this necessitates careful disinfection of all linen, &c., used in connexion with cholera patients. In short, cleanliness and good sanitary conditions are the first consideration in the treatment of cholera.

The enumeration of the above modes of infection at once indicates the method of prevention, by never drinking any unboiled or otherwise unsterilized fluid, and avoiding uncooked vegetables when cholera is prevalent. In addition to these obvious measures, there are certain prophylactic measures which should be taken on the occurrence of cholera. As it is so essentially a water-borne disease, the most important measure is the disinfection of the water supply. The older forms of sand and charcoal filters were worse than useless for this purpose, as they only served to accumulate the organisms, which multiplied in them, and infected any pure water run through. Thus in the terrible outbreak of cholera in a British regiment in Lucknow in 1894, when the troops were sent out into camp, their filters were taken with them, and kept up the disease until nearly one hundred men had been lost within a few days, the cholera

organisms being subsequently recovered from these filters. Only the finest grade porcelain filters are reliable, and in some of these bacilli have been found to grow through the pores within a few days, so they require frequent boiling. They must also be extremely well fitted at the joints to be reliable. Laboratory experience shows that only a certain proportion of those on the market give a sterile effluent even when new, and personally I should never care to trust to their efficiency during the prevalence of cholera. Boiling the water is simpler and more certain, if personally attended to and not left to a native servant. Hankin showed some years ago that the cholera bacillus dies out of aerated water within a few days, so unless this commonly consumed fluid can be obtained from a firm who can be relied on to sterilize the water employed in its manufacture, it is safer to keep it for several days before consuming it, if cholera is about.

Disinfection of Wells. In most parts of India the village, and to a great extent town water-supplies, are derived from wells, which are very liable to become infected during cholera outbreaks. Their disinfection, therefore, is a measure of the first importance, and much evidence has accumulated during recent years regarding the great value of permanganate of potash for this purpose. It appears to act rather by precipitating all organic matter in suspension than by actually killing the organisms, as the amount commonly used is not sufficient for the latter purpose. I am also in-

clined to think this oxidizing agent may owe some of its efficiency to destroying the toxins of the bacilli, and thus depriving them of their virulence, just as repeated washing does in the case of tetanus spores. The usual allowance is one or two ounces for an ordinary well, used in the following way. The salt is placed in a bucket or other convenient vessel and lowered gently into the water to fill it; it is then drawn up and the water poured carefully into the well without allowing the undissolved crystals to escape. This process is repeated until the whole has passed into solution, when the well water should have a faint pink colour which will disappear in a day or two, no harm will result from its being drunk at once. Indeed, the results of the administration of permanganates in the treatment of cholera, described later, suggest that the pink water may have some prophylactic effect in itself. During a recent outbreak of cholera in a district hospital in Bengal, in addition to disinfecting the well all the patients were given permanganate solutions to drink and no further cases of cholera occurred, so the drug would appear to be worthy of further trial for this purpose.

Predisposing Causes of Cholera

Chills. The older Anglo-Indian writers laid great stress on chills as an exciting cause of cholera. Thus, Annesley wrote: 'Although the disease cannot exist without some morbific condition of

the atmosphere, whatever that may be, sudden exposure to cold is its most common exciting cause, owing to the check which it gives to the capillary circulation on the external surface of the body.' Corbyn says: 'I do not hesitate to declare it as my decided conviction, that sudden check to perspiration is the immediate cause by which the effects witnessed in cholera are produced,' and Twining mentions 'a sudden decrease of temperature at night' as one of the exciting causes. The very low mortality frequently recorded in cases returned as cholera in those early days, however, proves that other forms of acute diarrhœa were not unnaturally confused with the specific disease. It is now well known that a chill at night, usually caused by the vigorous pulling of a punka by a wakeful coolie over one who has awakened in a profuse perspiration on account of the earlier cessation of the punkawalla's efforts, will produce an acute diarrhœa and vomiting, which may at first give rise to a suspicion of cholera, although this is soon allayed by its readily yielding to simple treatment. The writer had such an experience on first coming to Calcutta in the hot season, causing serious anxiety to a medical friend in whose house he was staying. The common custom in India of wearing a flannel belt round the abdomen at night—the so-called cholera belt—is to guard against such chills. Nevertheless, although a chill by itself will not produce cholera, yet it is easy to see that it may

powerfully predispose to the disease in any one who may have swallowed the specific organism, by producing congestion of the intestinal mucous membrane and more favourable conditions for the multiplication of the comma bacillus. The greater prevalence of cholera during unsettled weather, with rapid variations in the temperature, on which early writers lay so much stress, may thus be accounted for in some degree. Precautions against chills, especially from night punkas, are therefore well worthy of adoption, especially during any unusual prevalence of cholera.

Fasting. As the acid secretion of the stomach during digestion affords powerful protection against the passage of living cholera bacilli into the intestines, it is not surprising that draughts of infected water taken during prolonged fasting may readily excite an attack of cholera. As early as 1832, Corbyn wrote: 'Thus, in the city of Delhi, where the epidemic happened to prevail during the great annual feast of Ramazan, in which it is unlawful for Mohammedans to eat while the sun is above the horizon, a much larger proportion of persons of that persuasion suffered than of the Hindus, who were not similarly restricted as to the time of their meals.' This acute observation has since been amply confirmed, and in 1894 I met with cases in Lucknow during a cholera outbreak in which Mohammedan sepoys ate a big meal at sunset after fasting all day,

and were attacked by cholera in the early hours of the following morning, generally with fatal results.

Saline Purges during Cholera Prevalence. If the evacuant treatment in cholera of Sydenham and his contemporaries, which was so strenuously revived by George Johnson in the middle of the last century, is curative, then it might be expected that keeping the bowels freely open with salines during the prevalence of cholera would powerfully protect against infection by the disease. A strong consensus of Indian opinion, however, supports precisely the opposite view, namely that salines, especially given over night, greatly predispose to an attack of true cholera. Thus, Corbyn states that 'Many instances are noticed where cholera has supervened on the use of neutral purgative salts'. Twining also wrote: 'When cholera is prevailing in the vicinity, slight catarrhal or febrile affections and disorders of the stomach and bowels, whether tending to diarrhœa or constipation, seem convertible into cholera by the use of saline or drastic purgatives or cathartics, more especially if they operate about two or three in the morning.' He thought in such cases an insidious attack of cholera was going on before, which was brought on by purging persons who, if left alone, would not have had cholera, but he remarks that castor oil does not produce the disease. Ranald Martin, Morehead, and Macpherson all support these statements, the latter

remarking: 'This at least is enough to prove that purgatives do not avert cholera, and it is not very encouraging to their employment in its treatment.'

Visiting Endemic Areas. Another well-established fact regarding the incidence of cholera is the excessive liability of persons first coming from healthy areas to reside within endemic districts. H. M. Macpherson appears to have first established this point by showing that among Europeans in Calcutta, both of pure and mixed blood, only 24 per cent of the deaths from cholera occurred among the residents, while 76 per cent were in persons visiting or passing through the city, although this was not the case with other bowel complaints and fevers.

Race and Sex Incidence and their Relation to Mortality. Table IV shows the data I obtained from an analysis of the cases of cholera treated at the Calcutta Medical College Hospital from 1895 to 1905 inclusive, that is in the eleven years immediately preceding the extensive use of intravenous saline injections.

TABLE IV. RACE AND SEX INCIDENCE AND MORTALITY

	Died.	*Percentage.*	*Recovered.*	*Percentage.*	*Total.*	*Race Percentage.*
Hindus	497	61·6	317	38·4	814	69·9
Mohammedans . . .	150	57·3	109	42·7	259	22·2
Europeans and Eurasians	52	56·5	40	43·5	92	7·9
Native males	556	60·3	366	39·7	922	85·9
Native females . . .	91	60·3	60	39·7	151	14·1

The admissions of the different races are closely in proportion to their respective populations in Calcutta and thus show no special predisposition of any one race. On the other hand, more men than women are attacked in proportion to their numbers, doubtless on account of their occupations bringing them into closer contact with sources of infection.

The case mortality in different races is noteworthy. The death-rate is highest among Hindus, distinctly less among Mohammedans, and a little lower still among the European and Eurasian class admitted to the Medical College Hospital, who are nearly all permanent residents of Calcutta, who have also been born in India. The incidence is in proportion to the stamina of the different races and to the amount of meat eaten by them, and so indicates a greater resisting power to the terribly depressing effects of cholera. This relationship, as far as Europeans are concerned, only applies to those who have been bred or lived many years within the endemic area, the mortality among the emigrant class at the European hospital having been no less than 81·6 per cent in the thirteen years up to 1907 among 125 cases.

Even among native patients the case mortality is considerably higher in visitors to Calcutta from up-country provinces beyond the strictly endemic area, than in those born and bred in Lower Bengal itself.

The Sex death-rate is identical in Table IV for

both sexes, which is in accordance with my personal experience. The equally high mortality among the stronger male sex is probably due to the larger number of very severe cases met with among immigrant males.

Age Incidence and Mortality. Table V gives the age incidence and case mortality of cholera among Hindus and Mohammedans treated during the eleven years ending 1905 at the Calcutta Medical College Hospital.

TABLE V. AGE INCIDENCE AND CASE MORTALITY AMONG NATIVES OF INDIA IN CALCUTTA.

	Total Cases.	*Died.*	*Per-centage.*	*Re-covered.*	*Per-centage.*	380 *Cases with hypertonic saline.*	
						Died.	*Re-covered.*
0–10 years	36	19	52·8	17	47·2	31·2	68·8
11–20 „	156	80	51·3	76	48·7	28·3	71·7
21–30 „	468	274	58·5	194	41·5	24·2	75·8
31–40 „	273	174	63·7	99	36·3	36·7	63·3
41–50 „	111	77	69·4	34	30·6	39·0	61·0
Over 50 years	38	28	73·7	10	26·3	50·0	50·0

It is generally stated that cholera is particularly fatal in young children, but this has not been the case at the Calcutta Medical College during recent years, although very great care is required in their treatment. The lowest mortality occurred between the ages of 11 and 20, namely 51·3 per cent, and it steadily rose in each subsequent decade to reach 73·7 per cent, or almost half as high again, in persons over 50 years of age. In a smaller

number of cases in Europeans a similar relationship was found. The results with my hypertonic saline treatment are given in the last two columns of the table and show a greatly decreased mortality in each decade, which is most marked between the ages of 21 to 50 years.

CHAPTER IV

CLINICAL DESCRIPTION

ALTHOUGH cholera presents great variations in the degree of severity and, to a less extent, in the type of the disease, yet there is probably no acute specific infection which shows greater constancy in its principal manifestations. The sudden onset of profuse but painless diarrhœa, the stools rapidly becoming quite free from bile and fæcal matter, accompanied by copious watery vomiting followed by extreme prostration, with little or no pulse at the wrist, cold clammy skin, pinched face, with sunken, darkly encircled eyes, extreme restlessness, with frequent very painful muscular cramps and complete suppression of urine, all coming on within a few hours — constitute a picture which, once seen, never fades from the memory, and is only occasionally at all simulated by very acute summer diarrhœa of young children and some cases of ptomaine poisoning in adults.

For purposes of description the disease must be divided into different stages, which necessarily shade off into each other, although they are sufficiently distinct to require very different lines of treatment. A number of complications have also to be dealt with, by far the most important of which is the uræmic condition, which in some

degree or other is almost inevitable in those patients who remain long in the collapse stage of the disease, although its true nature was not clearly known to earlier writers on cholera.

Premonitory Diarrhœa

This stage is only met with in the milder types, being completely absent in the majority of cases seen in the tropics. It is nevertheless of great importance, as during the prevalence of cholera its early recognition may sometimes allow of suitable treatment preventing its passing on into a typical attack of the disease. The characteristic features of this stage are nausea or actual vomiting and the painless passage of bile-coloured stools, accompanied by great prostration and scanty urine, while the skin may be clammy and the pulse of low tension. Annesley further stated that in the stage of invasion an anxious expression of the face may be detected even before the patient feels unwell, and he goes on to describe how during a virulent outbreak of cholera on a ship at Madras the surgeon, as soon as he noticed any of his men depressed or low-spirited, at once bled them 20 to 30 ounces, administered calomel and opium, and sent them on shore to hospital, with the result that not a single one of a number of men so treated died of cholera! How many of these men were suffering merely from fright, which was promptly allayed by the confident, if heroic, measures adopted, would appear to be open to question.

Still, the moral of the incident, namely the great value of restoring confidence during epidemic cholera prevalence, remains true to this day.

According to Macnamara, premonitory diarrhœa is the exception rather than the rule in India, although it is said to be present in at least half the cases seen in Europe. It lasts from a few hours to a day or two, and is most frequent in the less acute forms of cholera. As Goodeve pointed out, it may last for some days, and be quite as copious as that produced by a few doses of castor oil, but still it may pass into profuse purging, collapse, and death, which he justly remarks should not be the case if George Johnson's evacuant treatment of cholera was correct. The importance of recognizing the premonitory diarrhœa of cholera is that it is generally held that it can usually be checked by astringents, including opium, and typical cholera thus prevented from ensuing: another fact which is at total variance with Johnson's now generally abandoned view. Moreover, the stools in this early and atypical form will contain the cholera bacillus and require as careful disinfection as in the fully developed disease, in order to prevent their becoming sources of its spread.

Stage of Copious Evacuations

The predominant feature of this stage is the great loss of fluid from the body through repeated copious vomiting and purging of a watery nature, producing marked shrinking of the body, sunken

eyes, and greatly lowered blood-pressure, this condition in severe cases passes insensibly into that of collapse.

Cholera Sicca is a term applied to a very rare and extremely acute form of cholera, in which fatal collapse takes place without any actual evacuations from the bowel. The very exceptional nature of this variety is shown by the experience of all Anglo-Indian writers. Thus, in Annesley and Twining's works I have not met with any reference to cholera sicca, while Corbyn only refers to it as a very rare form in which the vital powers are at once overwhelmed. Macpherson says he never met with it, and Goodeve remarks that in the most rapidly fatal cases there may be no purging, adding: 'But it does not follow that because there has been no purging there was no exudation into the intestines. The exudation is sometimes poured out and retained there, and we should never for a moment confound exudation with purging. In numerous instances in which there has been an absence of evacuations, post-mortem examination has shown the intestines full of fluid. . . . It is certainly not common for the practitioner in India to meet with these cases of absence of evacuation.' Macnamara quotes an experience of Sutton's of a man falling dead in the street without purging, whose intestines were found to be filled with fluid, although solid fæcal matter was present in the large bowel. He adds that death from cholera without vomiting or

purging is rare, and 'although the disease may kill very rapidly, no fatal case has ever been recorded where at least four pounds of serous fluid have not passed from the blood-vessels into the intestinal canal'. In a recent medico-legal post-mortem on account of sudden death, great distension of the small bowel with choleraic stools was found. Clinically, it is sometimes possible to detect physical signs of a large quantity of fluid within the abdominal cavity, as Wall pointed out. The very rapid loss of several pints of fluid into the intestines may obviously be more fatal than the gradual evacuation of a much larger quantity through repeated vomiting and purging spread over some days, as in the latter case much of the loss may be replaced by absorption from the tissues or by fluid given by the mouth and rectum. A much truer idea of the effects of the drain of fluids from the body in cholera can be obtained from an estimation of the percentage lost from the blood, to be described on p. 147.

Quantity of the Evacuations. As cholera patients usually only come under observation after copious vomiting and purging have taken place, it is seldom that the amount of fluids lost can be directly measured. Corbyn writes: 'To those who have not seen persons labouring under this disease, it will not be easy to convey an idea of the enormous amount of these discharges. It seemed as if the whole of the fluids of the body would have been insufficient for their supply;

and that they very sensibly diminished the mass of blood was shown by its thickness and unwillingness to flow upon a vein being opened; and by the uniform check given to all secretions. The evacuations were sometimes poured forth in a continuous stream, as if from a sluice; at others, ejected in small volumes, as if from a syringe, by the violent action of the stomach and rectum.' Goodeve remarks: 'So excessive are these evacuations, that in two or three hours, or less, an ordinary stool-pan will be nearly filled' (eight pints or more in capacity). Macnamara mentions that a quart may be passed within a few seconds, while Wall writes: 'The diarrhœa is profuse, it literally pours from him in a continuous stream.' The vomiting may be almost as copious, for I have seen a quart ejected at one time, although little fluid had been recently given by the mouth. Macnamara refers to a dropsical patient of Dr. Barlow's, who, during an attack of cholera, passed gallons of liquid stools without his pulse disappearing, and he eventually left hospital apparently well, but with his skin hanging loosely upon him.

Characters of the Evacuations. The essential feature of typical cholera stools is the entire absence of bile once the bowel has been cleared of its original contents. They consist of an opalescent colourless fluid, with a faint but somewhat characteristic odour, and are commonly described as rice-watery, on account of their re-

semblance to water in which rice has been boiled. This appearance is due to the presence of fine granular matter in suspension, while on standing larger white flakes of epithelium fall to the bottom, sometimes leaving clear supernatant fluid. In severe attacks the fluid may be pink, owing to the presence of blood. Such cases are often accompanied by severe abdominal pain and commonly terminate fatally. A pink discoloration of the stools, however, is not necessarily of bad prognostic import, as I have repeatedly seen recovery take place. If the disease progresses favourably a decline in the frequency and copiousness and an increase in the consistence of the stools is accompanied by the reappearance of bile in them. They may thus become light yellow, but more frequently of a green tinge, which may reach quite a deep tint, and is then a favourable prognostic indication, as I have very rarely seen such cases relapse. In very mild attacks, especially such as occur at the end of an epidemic prevalence of cholera, the stools may never quite lose their colour, and yet contain the comma bacilli, their recognition is therefore important in order that the evacuations may be disinfected without delay.

Microscopically, the opalescence of the stools is seen to be due to the presence of fine granules derived from broken down epithelial cells. The sediment may show masses of epithelial cells with marked granular degeneration, together with some mucus, but it is often surprising how few

complete cells are seen. Innumerable micro-organisms are present, which have been dealt with under the head of bacteriology on p. 57. Numerous blood corpuscles are sometimes present, but leucocytes are not very numerous.

Vomiting. This symptom nearly always appears at about the same time that the copious evacuations of the bowels commence. It is very variable in degree, and I have even seen it absent during several hours' observation in hospital, even in acute cases terminating fatally. It is usually a persistent symptom, although often it does not appear to cause as much distress as might be expected. Once the contents of the organ have been expelled, the vomit is very watery in nature, and commonly copious in amount. In fact, the vomiting of much watery fluid, when but little has been swallowed, is one of the most pathognomonic features of cholera. When very copious it does much to exhaust the patient, and may indeed be an important factor in producing collapse. On account of the terrible thirst, the patient calls repeatedly for water, only too often to reject it almost at once, together with any medicine which may have been given. Nothing, however, is more cruel and unnecessary than to withhold water from those in the throes of cholera, while there can be little doubt that some of the toxins are removed from the body through the active secretion of watery fluid by the stomach. Moreover, by giving small quantities of fluid to drink at a time it is surprising how much will be

retained and absorbed, greatly to the relief and benefit of the patient. It is to be noted that vomiting in cholera commonly causes surprisingly little distress.

Hiccup may exceptionally be a very troublesome symptom, but my own experience is in agreement with that of Morehead, Wall, and others, in regarding it as not a particularly unfavourable symptom.

Abdominal Pain is frequently referred to by the older writers. Annesley mentions a burning sensation about the navel; while Corbyn writes: 'The patient always complains of pain across the abdomen, which is generally sore to the touch, and swelled from the scorbiculus cordis to the pubes, sometimes hard and knotted, and drawn back towards the spine. The burning sensation of the stomach and bowels was always present.' These pains are partly due to cramps of the abdominal wall, but the burning sensation may also be very severe, and if persistent, and especially if accompanied by hæmorrhagic stools, is of serious prognostic import. It may be present at a very early stage, as remarked by Goodeve, and be associated with an anxious expression of the countenance.

Muscular Cramps. These commence in the stage of evacuations, but continue and are most severe during marked collapse. According to both Corbyn and Twining, the cramps begin in the fingers and toes, extending up the arms, calves of the legs,

and thighs, to reach the abdomen and lower part of the thorax. Annesley notes that the muscles of the back and face are uniformly exempt from them. They cause great pain and produce a hard knotty feel of the muscles affected, being more marked in muscular Europeans than in the less developed natives of India. They are most severe and distressing in patients who are pulseless and cyanosed, which, taken with their appearance in the distal parts of the extremities, points to their being caused by the deficient circulation of very venous blood. In such cases the older observers usually found it impossible to abstract more than a few drops of extremely thick black blood from the median basilic vein in their attempts to bleed their patients. I have always found that as the pulse becomes restored and cyanosis disappears during intravenous saline injections, the agonizing cramps disappear, often after only a pint or so has been run in, and the patient commonly falls asleep before the process is concluded. In fact, the immediate relief thus afforded constitutes the presence of severe cramps a most important indication for transfusion.

General Condition in Stage of Evacuation. As a result of the rapid loss of fluid from the body the characteristic condition of cholera patients quickly ensues. The surface temperature falls below normal, commonly reaching 95° to 96° F., or even lower. Except in extreme cases, the internal heat of the body is, however, retained, so

that the rectal temperature is about 99° and often higher, a point which will be dealt with further in speaking of the reaction stage. The skin, in addition to being cold and clammy, has a shrivelled appearance and is said to lose its elasticity and feel doughy. The head and neck may be bedewed with cold sweat. The finger nails, and in bad cases the lips, become cyanosed, while a dark ring is seen around the sunken eyes. As Wall pointed out, the tongue, in addition to being dry, may actually be cold to the touch, a condition which is best estimated with the dorsum of the middle digital phalanx. Extreme thirst is a most distressing symptom. The pulse has by this time become very small and of extremely low tension, while the rapidity of the beat is increased to 100 or more a minute.

The **Blood-pressure**, according to my observations, is below 70 mm. at the wrist in the majority of the patients on admission to hospital, and commonly as low as 50 to 60 millimetres. In extreme collapse it is too low to be measured at all at the wrist, such cases forming over one-third of the admissions to Calcutta hospitals. These observations were mainly made on native patients whose normal blood-pressure is only from 100 to 120 mm. In some European patients equally marked loss of pressure was also met with as a rule.

Suppression of Urine ensues as soon as the evacuations have induced a marked fall in the blood-

pressure, it is therefore present for a time, at any rate, in all but the mildest cases of cholera; being an important symptom, as it is less frequent and sustained in other forms of diarrhœa. That the failure of the kidneys to secrete is directly due to the deficient blood-pressure, is clear from the fact that free secretion of urine frequently ensues within a few hours of the full restoration of the circulation by copious hypertonic transfusions.

The Stage of Collapse

In the milder cases of cholera, which constitute about one-third of the whole in Calcutta, a low pressure but fair pulse persists throughout the attack, and collapse does not occur. In the remaining two-thirds this serious symptom ensues with greater or less rapidity and degree. The pulse becomes only just perceptible or entirely lost at the wrist; the voice sinks to a hoarse whisper; the coldness of the skin becomes very marked, the axillary temperature being commonly below 96° and sometimes even much lower; the shrivelled and cyanotic appearance of the fingers reveal the entire failure of the circulation to reach the distal portions of the extremities; severe muscular cramps continually torment the patient, while great restlessness and jactitation eloquently testify to the speechless agony of the sufferer, rendered all the more acute by the preservation of the intellect to the bitter end, and he cries for relief to the physician, who has for so long been nearly powerless to

help him in his distress. Drugs are now useless, if only because the circulation has failed too much to allow of their absorption from the seriously damaged intestinal tract, while repeated experience of the past eighty years has shown that the restoration of the circulation by normal saline injections, after working the apparent miracle of snatching the patient from the brink of the grave, is usually of but very temporary benefit, a fatal recurrence of the collapse too often appearing within a very few hours.

The collapse usually gradually follows the stage of copious evacuations, but it may be reached by a sudden failure of the circulation after the passage of a large watery stool or a copious vomit, so the pulse should always be carefully noted after these occurrences, to detect any marked fall in blood-pressure as soon as possible, and allow of immediate steps being taken to avert a total failure of the circulation. During actual collapse the stools and vomiting usually become less frequent and copious, although smaller watery evacuations continue from time to time. This apparent abatement in the most urgent symptoms may possibly mislead the inexperienced, if the blood-pressure is not closely watched, for the lessened secretion by the bowel may be only due to the great failure of the circulation and concentration of the blood, and so be an unfavourable rather than a good sign. This view is borne out by the fact that intravenous injections of normal

saline solution are usually followed by renewed copious rice-water stools. In extreme cases no pulse may be perceptible even in the brachial artery, such cases being practically always fatal, according to the older writers, although I have seen them recover under the treatment described in a later section.

Duration of the Collapse Stage. This may vary from a few hours to two days, in accordance with the severity of the disease. According to Goodeve, if the algid stage does not last more than eight to ten hours. a regular convalescence may be expected, but if it runs to eighteen or twenty-four hours, should the patient survive the stage of reaction, there will be greater danger from secondary risks. Macnamara puts the collapse stage at twenty-four hours, if not fatal earlier, the mortality being very high, especially in those past the prime of life. All writers agree that the longer the collapse lasts the greater the danger of serious later complications, and especially of uræmia. Too much stress cannot be laid on the importance of unremitting watch over patients suffering from cholera, for the suddenness with which a fairly good pulse and hopeful outlook may pass into dangerous collapse, urgently calling for energetic measures, is very soon brought home to those who have to treat this disease. I have several times seen a patient admitted with a fair pulse and general condition, and a blood-pressure of over 70 mm., who within a few hours had become

dangerously collapsed, or had even died too quickly to allow of the measures necessary for restoring the circulation.

Stage of Reaction

If the collapse stage is survived the pulse begins slowly to regain its strength, with a corresponding rise of blood-pressure; the surface temperature rises to normal, and nearly invariably goes on to reach a higher degree, the warmth of the extremities at the same time returning and the reaction stage is entered on. The stools now become less frequent and copious, first becoming thicker, and sometimes almost milk-like in appearance, and then coloured green or yellow, owing to the reappearance of bile in them. The vomiting ceases, all restlessness passes away, and sleep may at last be obtained by the worn-out patient. An anxious watch must now be kept for the reappearance of free secretion of urine, which will give good hope of a speedy convalescence. The possibility of its retention in the bladder must be borne in mind and guarded against, while the quantity passed should always be carefully measured. If the collapse has been slight and of only a few hours' duration, the secretion of urine may become re-established within twelve to twenty-four hours. In more severe cases, with prolonged collapse, this may take two or three days and yet ultimate recovery may take place, although such cases cause great anxiety from threatening uræmia. In fact, the frequent occur-

rence of excessive febrile reaction and uræmic complications led the older Anglo-Indian writers to regard the stage of reaction as not less dangerous than choleraic collapse itself, thus they demand special consideration.

Excessive Febrile Reaction. Norman Chewers described cholera as a fever in which the rise of temperature is masked during the collapse stage by the failure of the circulation through the peripheral parts, becoming apparent during the reaction period of the disease. I am convinced that there is much to be said for this view. Except occasionally in very mild cases some rise of temperature occurs during reaction. In those recovering without transfusion it usually only reaches from 100° to 102° in the axilla in native patients (see Chart 1, p. 105). In Europeans this rise of temperature is still more marked and frequently reaches a dangerous point apart altogether from the use of intravenous or subcutaneous salines. This point can best be illustrated from an analysis I have made of all the cholera cases treated in the Calcutta European hospital from 1895 to 1906, that is before the revival of intravenous injections, when the mortality was no less than 81·6 per cent. Of the ninety-four deaths, 62 per cent took place in the collapse stage, 23 per cent during reaction, and 15 per cent from uræmia. Thus, after collapse, excessive reaction was the principal cause of death, being half as fatal again even as the dreaded uræmic complication. Much light is thrown on

the causation of this high mortality by a study of the temperatures recorded, all of which are axillary or mouth readings, mainly the former. They are shown in Table VI, the last column giving those in which no salines, not even by the rectum, were administered.

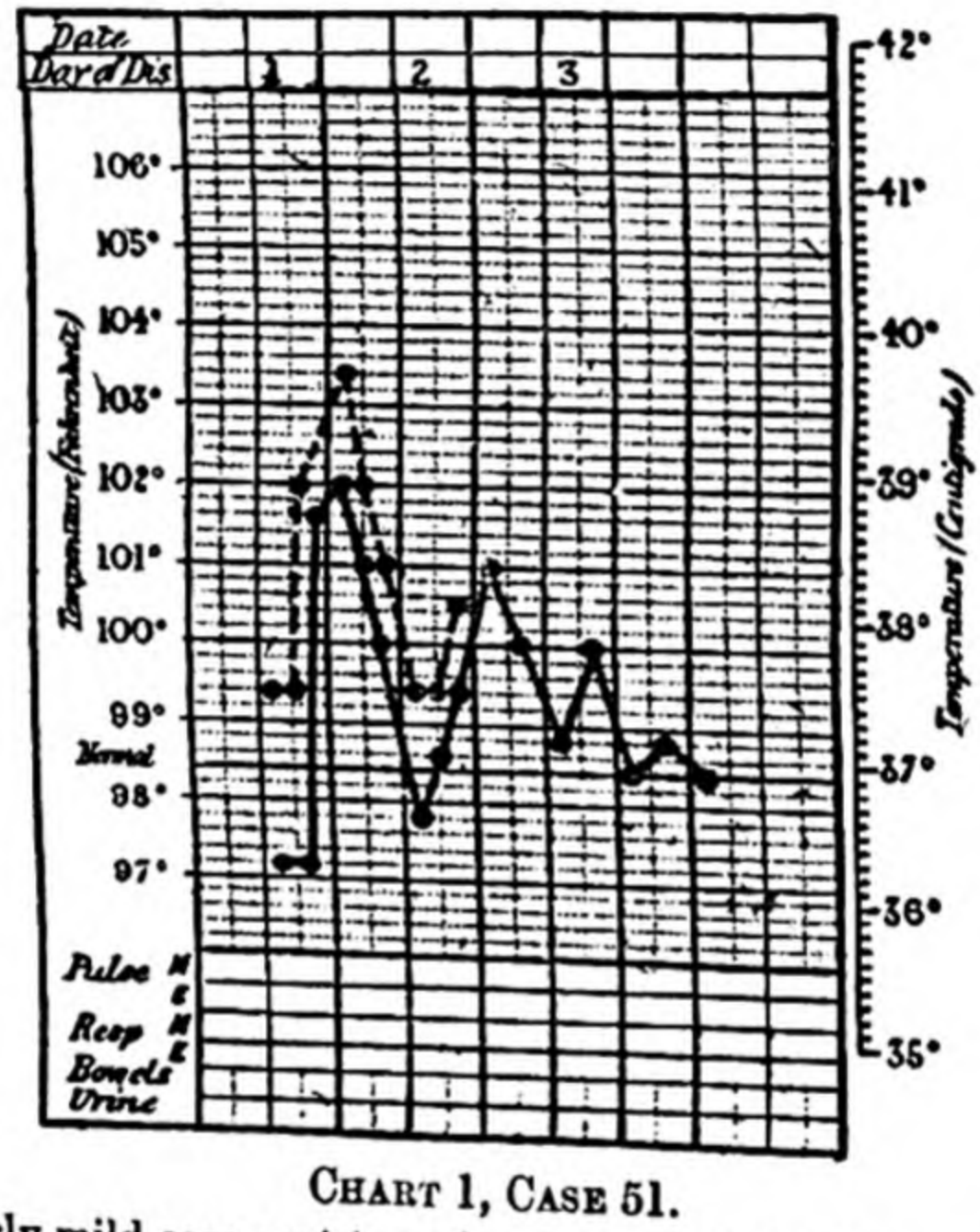


CHART 1, CASE 51.
Fairly mild case, not transfused, marked febrile reaction.
Dotted line = Rectal temperature.
Continuous line = Axillary temperature.

These figures are very striking, for they show that in no less than nineteen out of the twenty-two cases proving fatal in the reaction stage the temperature rose to 103° F. or over, while in ten it reached the hyperpyrexial point of from 105° to 106·8° F., although only one of these last had received any saline injection. Thus, fatal excessive febrile reaction was the most frequent cause of death in

those Europeans who survived the collapse stage of cholera even when no saline injections had been given, and this hyperpyrexia caused 28 per cent of the deaths in the reaction period. This mortality is clearly due to absorption of a fatal dose of toxins from the bowel with the revival of the circulation, for apart altogether from actual hyperpyrexia, every European patient during the eleven years under review, whose temperature rose to over 103°, died in the reaction stage.

TABLE VI. TEMPERATURES IN EUROPEAN CHOLERA CASES FATAL IN THE REACTION STAGE.

Highest Temperature.	*Total Cases.*	*Cases receiving no Saline Injections.*
Below 103° F. . .	3	2
103–104° F. . .	4	3
104–105° F. . .	5	2
105–106° F. . .	7	6
106° and over . .	3	3

The practical importance of the above facts cannot be exaggerated now that intravenous salines are again being largely used in the treatment of cholera, for these injections are always immediately followed by a marked rise of temperature in all but moribund patients (see Charts 2, 3, and 4, p. 107), and the early artificial reaction thus induced may occasionally pass beyond control (see Chart 6, p. 109). This is not surprising when we remember that hyperpyrexia so commonly occurs in cases which are not so severe as to prove fatal in the collapse stage, for many of those which are rescued

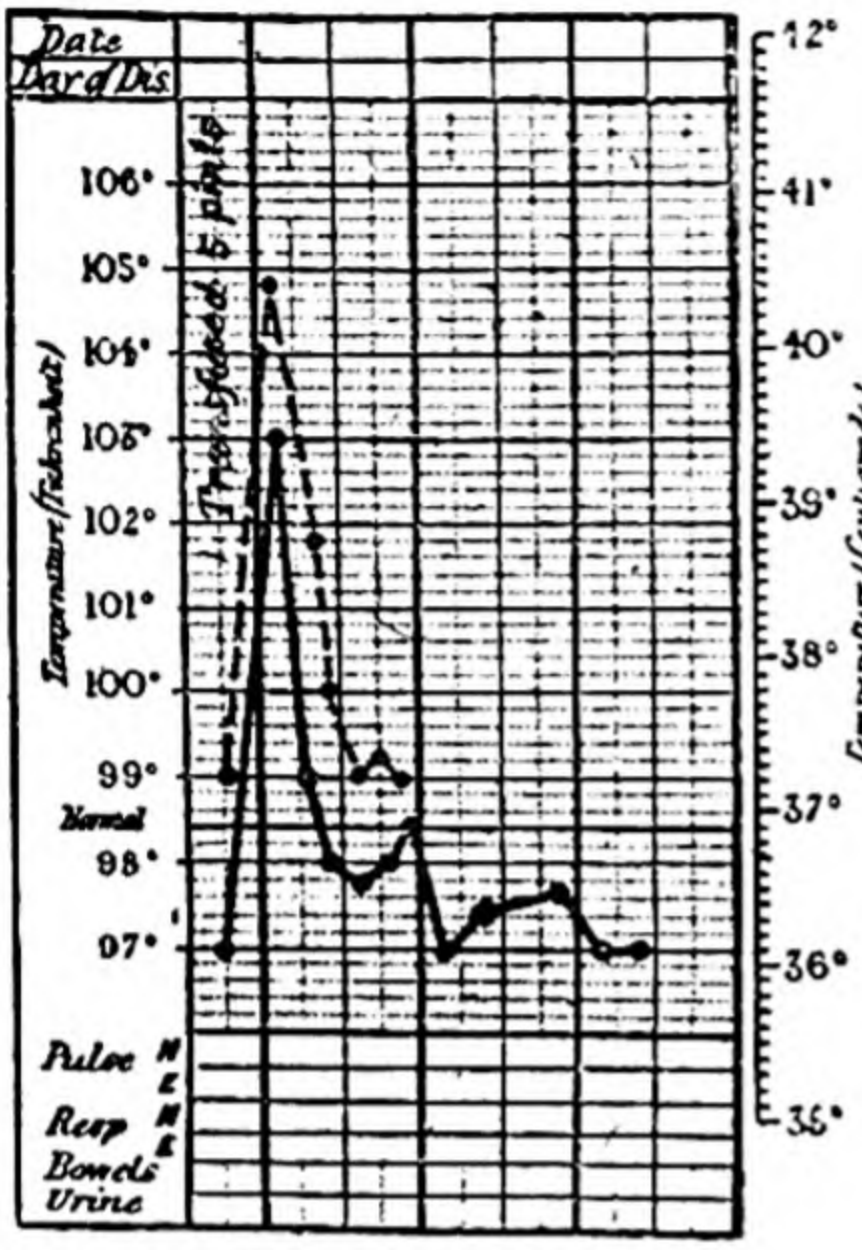


CHART 2, CASE 22.
Short febrile reaction after hypertonic saline intravenously.

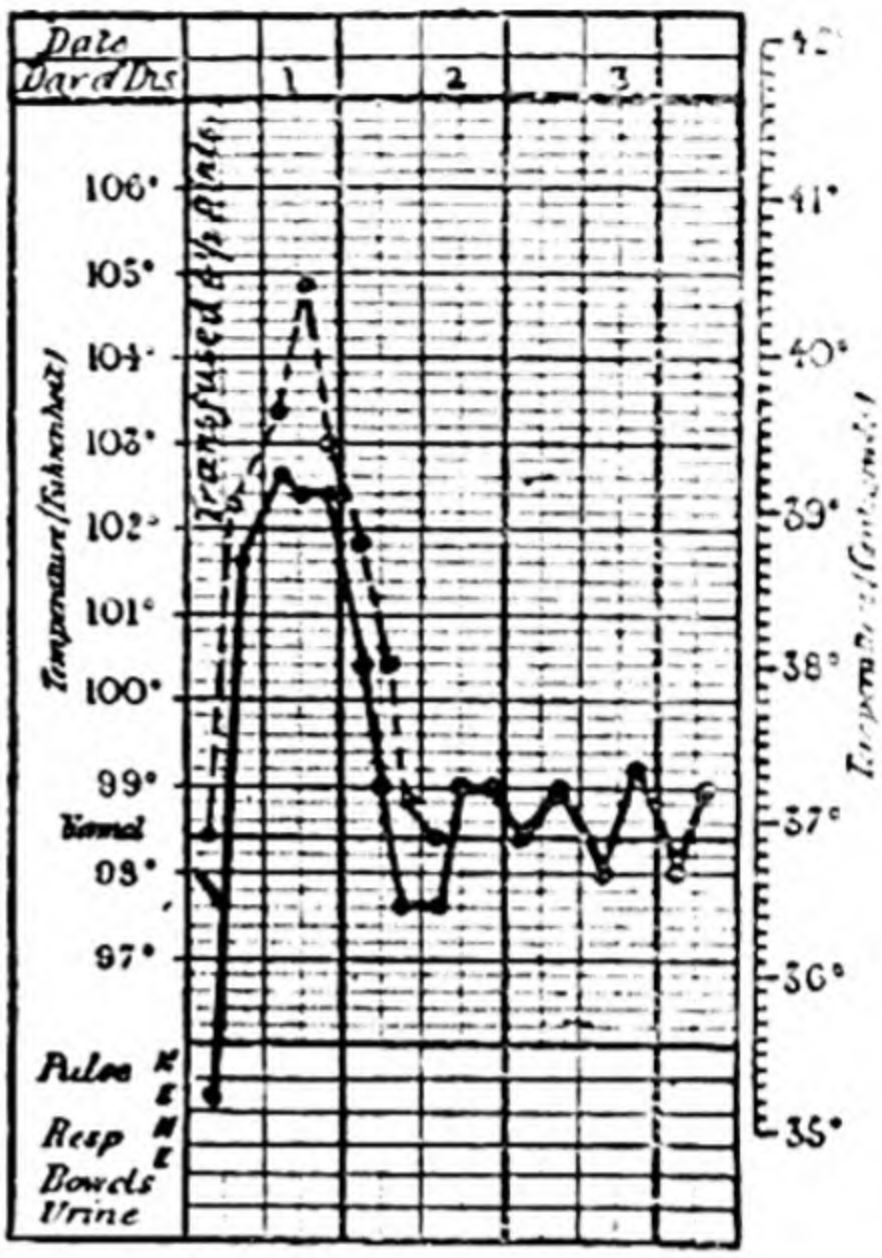


CHART 3, CASE 19.
More prolonged febrile reaction after hypertonic saline intravenously.

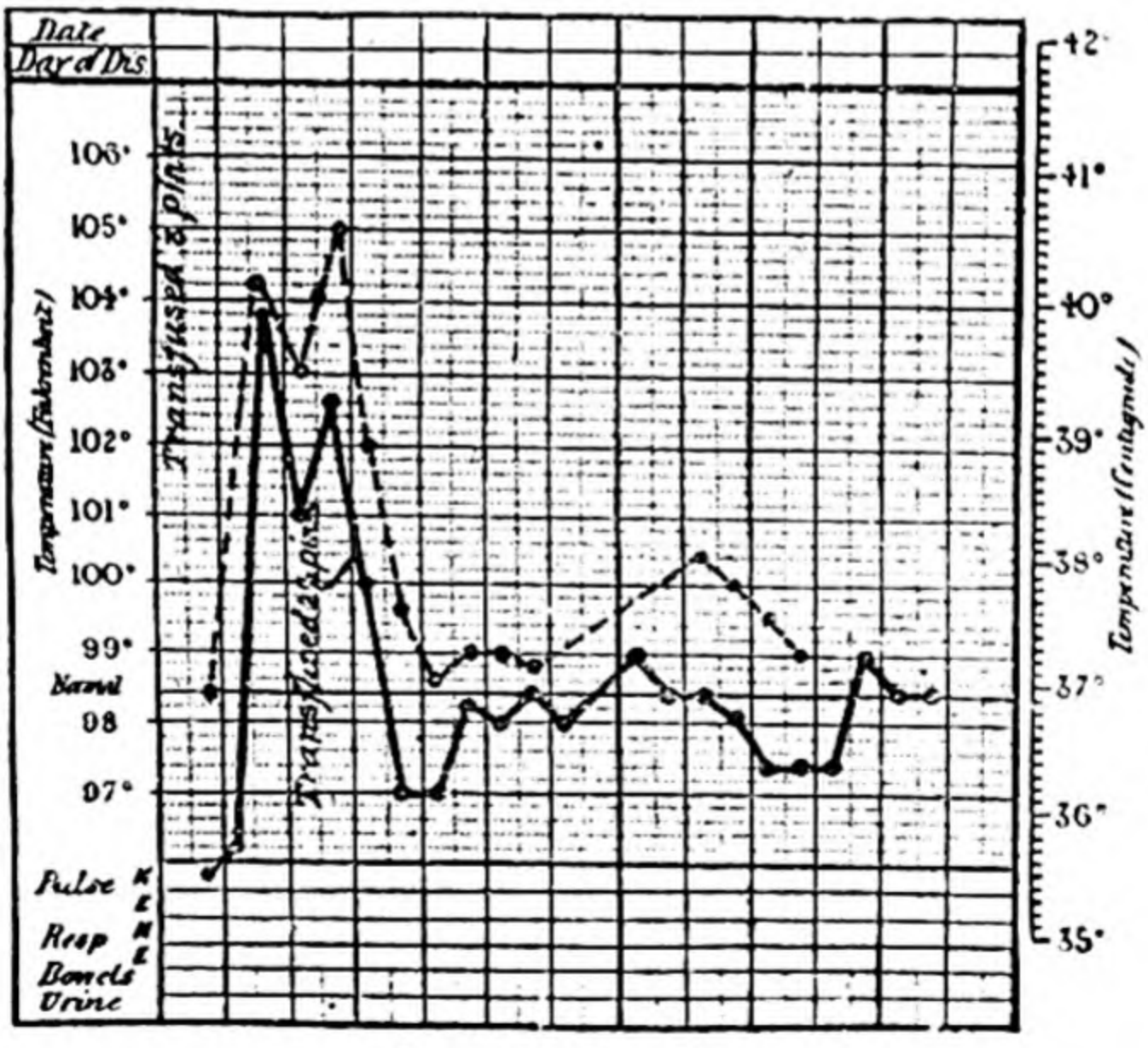


CHART 4, CASE 67.
Febrile reaction after two hypertonic saline injections given within twelve hours.

from death from collapse by saline injections are much more toxic in nature than the former, and so are more likely to show excessive reaction. Experience, however, has shown that a rigor and a rise of temperature to considerably over 103° F.

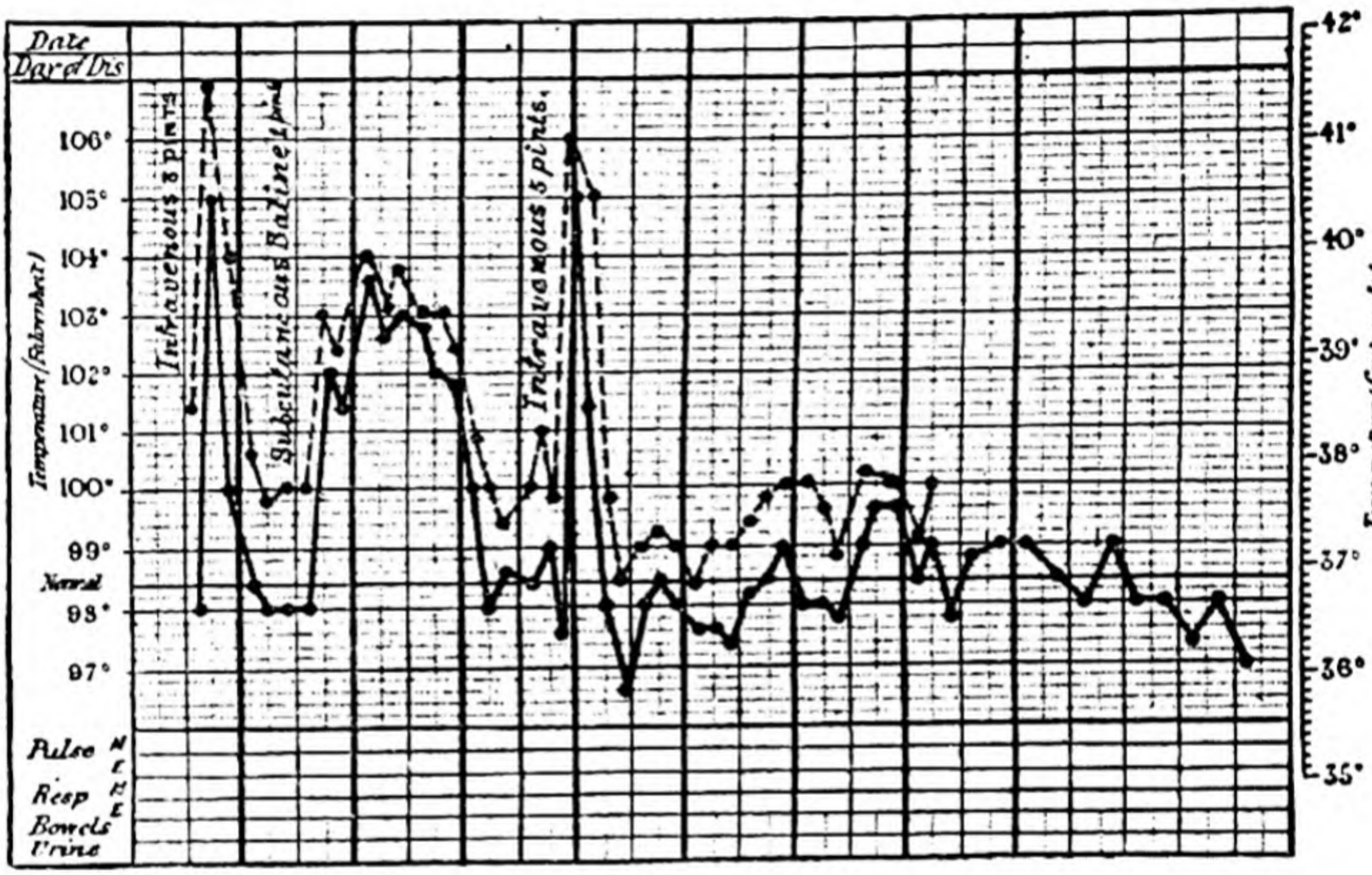


CHART 5, CASE 78.

Hypertonic saline given intravenously at a temperature of 36° Cent. in a patient with a high rectal temperature on admission, followed by temporary hyperpyrexia and a secondary rise the next day. A second intravenous injection was given for a relapse on the third day.

following an intravenous injection is not serious if it is of short duration (see Charts 5 and 7, pp. 108, 110), but it is essential to have the means described under the treatment of the reaction stage, ready at hand to control the fever without delay. Means whereby excessive febrile reaction after transfusion can be largely prevented are also described later.

If high fever is accompanied by complete loss of consciousness and delirium the prognosis becomes exceedingly grave, for although the temperature may be reduced I have never seen return of consciousness and recovery from this condition. This also indicates that the process is essentially due to absorption of an excess of toxins, for in hyperpyrexia of heatstroke recovery commonly ensues if the unconscious state has not lasted over one and a half hours, as I have shown in my work on '*Fevers in the Tropics*.'

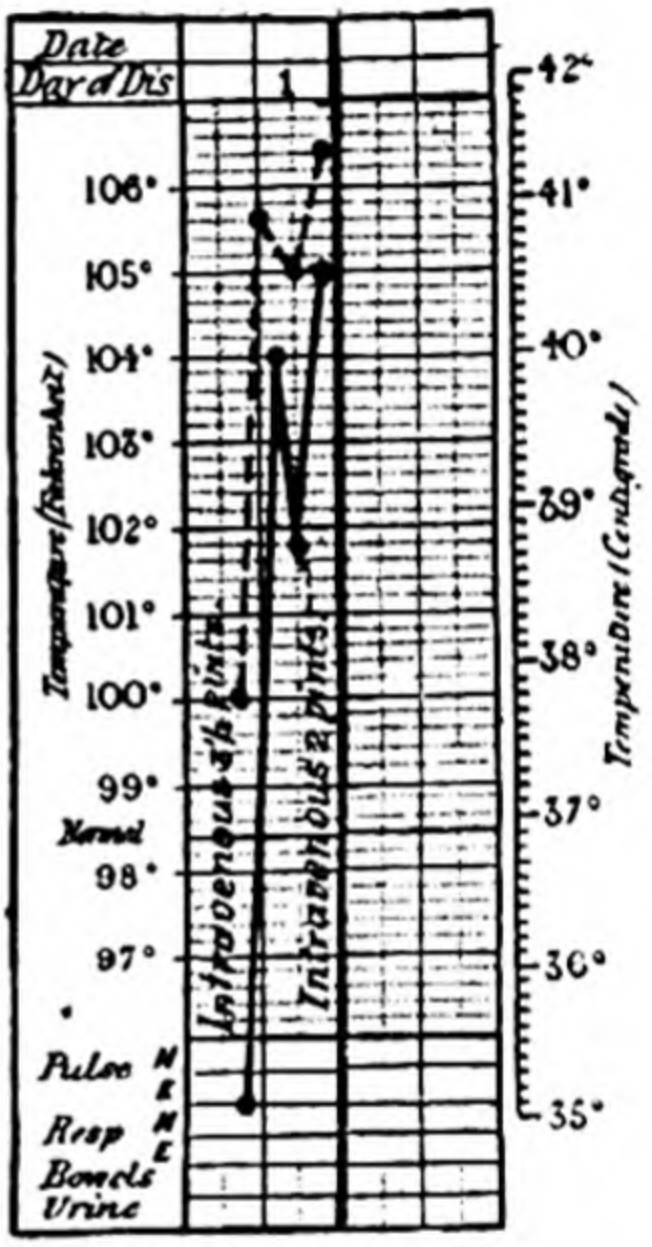


CHART 6, CASE 76.

Fatal hyperpyrexia following two transfusions at 37° C. in a very severe case.

In addition to the hyperpyrexial form of reaction, a less common typhoid-like form occurs, in which the temperature persistently remains high, even although no saline injections may have been given, such as at about 103° for two or more days; these cases are very fatal and difficult to deal with, especially if accompanied by symptoms of uræmia, as is often the case.

The **Urine** has been carefully examined in the Philippine Islands by Nichols and Andrews, who found albumen always present in considerable amount during the first two or three days, after which it decreased in recovering cases, but re-

mained high in those developing uræmia. The urea was very small in amount during the first two days, but steadily increased from the third day in recovering patients, while it remained scanty in uræmic ones, as did the total solids and the quantity

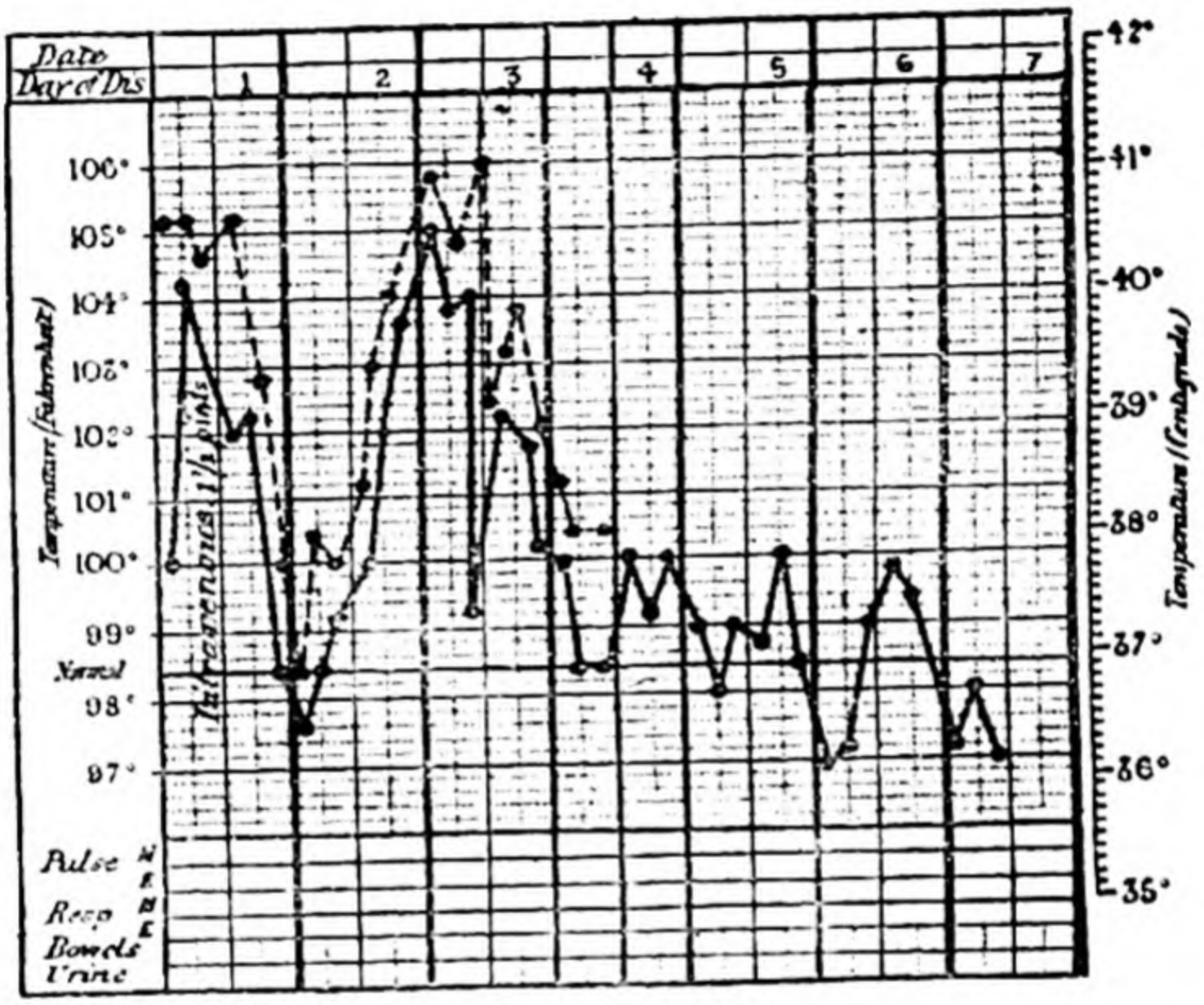


CHART 7, CASE 83.

Case admitted pulseless with a rectal temperature of 105·2° F. Intravenous hypertonic saline given. Recovery.

passed. They summarize their results in the following table showing the average in each class :—

	Quantity of Urine.	*Albumin.*	*Urea.*	*Total Solids.*
Recoveries	900 c.c.	0·3	13·0	18·0
Deaths	72 c.c.	2·0	0·7	2·0

The average time of convalescence was five days, while the average fatal case lived six days.

Uræmia

The most justly dreaded late complication of cholera is continued suppression of urine after reaction from collapse has taken place, as unless it be of strictly limited duration it leads to the supervention of uræmia combined with toxæmia. Writers in the early part of the nineteenth century described the symptoms of this condition without fully realizing their causation, but for many years past their significance has been completely understood. All experienced writers are agreed that the danger of continued failure of the secretory functions of the kidneys is in proportion to the duration and severity of the collapse stage of the disease. I have found it to be most frequent in two classes of cases. Firstly, in patients who have been admitted within the first twelve hours of the onset of a very severe attack and tided with great difficulty over a long collapse period by means of one or more intravenous injections. Secondly, in patients admitted as a rule forty-eight hours or more after the onset of a comparatively mild attack, but who have been without the advantages of skilled treatment and have often not been seen by a medical man. In both cases there has been prolonged suppression of urine and stasis of the renal circulation, making the restoration of the functions of the kidneys a difficult matter. It is interesting to note that the case-mortality was also highest among the

early and late admissions, as pointed out by Morehead.

The **Symptoms** do not materially differ from uræmia due to other conditions, although its course is a more rapid one, as it affects those who have just passed through an exceedingly depressing and acute disease, while it is aggravated by the retention in the system of some of the cholera toxins which should be mainly excreted through the kidneys. After reaction has set in, the bladder remains empty or only a very few ounces of urine are passed and within a day or two symptoms of toxæmia become clearly evident. The pulse remains above the normal rate and tends to increase instead of falling. More important is a quickening and deepening of the respirations in the absence of any lung complication, which should at once put the physician on his guard and lead to the adoption of vigorous measures to try to avert the threatening calamity. Vomiting may recur, but it is not usually a marked symptom in my experience. The skin is dry, and sweating may sometimes be difficult to produce in unfavourable cases. Diarrhœa may persist, and I agree with Goodeve's advice that it should not be checked, as it may carry off some toxic substances, although it has the disadvantage of tending to lower the blood-pressure. I have seen lead acetate given for late diarrhœa in a patient passing somewhat scanty urine, followed by complete and fatal suppression of urine, although the original attack of cholera had

not been a particularly severe one. If the action of the kidneys cannot be restored the respirations become more and more laboured, restlessness ensues, and after a struggle for breath, sometimes lasting for several days, gradual clouding of the intellect, deepening into coma or cardiac failure, ends the scene.

Frequency of Uræmic Complications. The great importance of these serious complications will be seen from the fact that during 1907, at the Calcutta Medical College Hospital, the mortality from uræmia was 13·2 per cent of the total admissions, or nearly one-fourth of the total deaths from cholera. In the Philippine Islands, of the patients surviving the collapse stage 28 per cent died of uræmia. It is particularly trying to the physician, after tiding a patient over serious cholera collapse, to lose him from this terribly distressing complication, the prevention of which is scarcely less important than the successful treatment of collapse. Fortunately, a study of the circulatory conditions associated with post-choleraic uræmia has both thrown great light on its true causation, and enabled its probable occurrence to be foreseen sufficiently early to allow of active measures for its prevention being successfully taken in the majority of cases, the mortality from this cause having been reduced by one-half during the last two years, namely to but 7 per cent of the admissions.

Relationship of the Blood-pressure to Post-Choleraic Uræmia. While making daily observa-

tions of the blood-pressure in cholera I noticed that if it remained below 100 mm. in adult males for two or three days after the collapse stage was over, uræmic symptoms almost invariably developed and proved fatal unless the blood-pressure could be raised to over 105 mm. Thus in ten fatal uræmic cases during 1908, following severe attacks of cholera necessitating intravenous saline injections, in five the blood-pressure at the end was only about 80 mm., in three more it was not over 90 mm., while in only two did it reach 100 mm., and that only immediately after transfusion two to five days before death. During 1909 very careful daily readings showed that every case in which the blood-pressure remained permanently below 100 mm. died of uræmia, while no cases in which it rose to over 105 mm. succumbed to renal complications. I have since met with occasional cases in which uræmia proved fatal in spite of higher blood-pressures having been obtained, but in those in which a post-mortem was obtained some antecedent organic disease of the kidneys was usually found, such as granular contracted kidney or stricture of the urethra with back-pressure effects.

These observations, together with the results of microscopical examinations of the kidneys in fatal cases (see p. 140), led me to suspect an actual mechanical obstruction to the circulation through the kidneys as the cause of continued suppression of urine during the reaction stage of cholera. In

order to test this hypothesis I carried out a series of post-mortem perfusions of normal salt solution through the renal circulation both on healthy kidneys and those of patients who had died of choleraic uræmia. The results were very striking, for whereas in normal organs a pressure of 20 to 30 mm. mercury sufficed to run a good stream through the renal circulation, in those obtained after death from the uræmic complications of cholera 80 to 100 mm. pressure were required for the same purpose. This proved the presence of grave mechanical obstruction to the circulation through the organ, which was sometimes found to be due to actual hæmorrhages into the substance of the organ, causing it to be tightly encircled by its capsule. In some instances splitting and peeling off the capsule enabled the salt solution to be perfused at 10 to 20 mm. less pressure than before decapsulization. As presumably a somewhat higher pressure would be required during life to force the blood through the renal circulation than to perfuse salt solutions after death, it is clear from these experiments that little or no blood stream can be passing through the kidneys during the reaction stage in those cases of cholera in which the blood-pressure remains permanently well below 100 mm., and the continued suppression of urine is at once explained. The practical importance of this discovery is also evident, as it indicated the necessity of raising the blood-pressure to over 100 mm. at as early a period as possible in cholera,

in order to prevent the stasis of the renal circulation, with its inevitably continued abeyance of the renal functions.

Relationship of a High Specific Gravity of the Blood to diminished Urinary Secretion. Another very important point is the degree of concentration of the blood, for it will be evident that when the specific gravity of this fluid is much above the normal it will both circulate less freely through the kidneys and also allow of greatly diminished escape of secretion owing to from one-half to two-thirds of the fluid of the serum having been lost. Until the blood has been once more diluted to its normal consistency free secretion of urine is not to be expected. Thus a high specific gravity of the blood, accompanied by greatly diminished urinary excretion, is an indication for dilution of the circulating fluid in some way or other, even although the blood-pressure may be about normal, for sufficient may not be absorbed by the alimentary tract in time to prevent fatal renal stasis and uræmia ensuing.

The practical importance of the foregoing observations can scarcely be exaggerated, it will be well therefore to illustrate them further by cases in point. For convenience of reference they have been embodied in Table VII, which shows the daily ounces of urine, blood-pressures, and specific gravities of the blood arranged so as to allow of the relationship of the last two on the renal activity to be seen at a glance.

TABLE VII. RELATION OF BLOOD-PRESSURE AND SPECIFIC GRAVITY TO URINE EXCRETION.

		Days after admission.				
	Sp. Gr.	1060	1057	1055		
1.	mm. B. P.	80	108	110		
	oz. Urine	0	19	98		
	Sp. Gr.	1066	1063	1055	1056	
2.	mm. B. P.	88	112	116	116	
	oz. Urine	0	1	42	82	
	Sp. Gr.	1071	1063	1056		
3.	mm. B. P.	82–88	92	112		
	oz. Urine	6	13	60	106	
4.	mm. B. P.	0–35	100	95	115	
	oz. Urine	12	38	8	38	116
	Sp. Gr.	1068		1062		
5.	mm. B. P.	65–97	102	92	108	115
	oz. Urine	40	56	5	32	122
	Sp. Gr.	1065	1054	1065	1056	
6.	mm. B. P.	0–95	103	88	102	
	oz. Urine	15	40	4†26	100	
	Sp. Gr.	1063	1058	1055	1051	
7.	mm. B. P.	0–75	83	85	95	
	oz. Urine	0	6	11	34	47
	Sp. Gr.	1064	1046	1044	1044	
8.	mm. B. P.	84–97	102	115	118	
	oz. Urine	½	6	40	150	

1. Mild case not transfused. Recovery without uræmic symptoms.

2. Fairly mild, not transfused. Subcutaneous saline second day for high specific gravity and deficient urine.

3. Very severe. Two transfusions first day and subcutaneous saline second day for deficient urine. Recovered.

4. Extremely severe. Three transfusions first day and one on third day for deficient urine.

5. Severe, transfused. Low blood-pressure third day. Vaso-constrictors. Recovered.

6. Very severe. Two transfusions first day and one on third day for deficient blood-pressure. Recovered.

7. Very severe in boy. Two transfusions first day. Two subcutaneous salines later for deficient urine.

8. Admitted pulseless and uræmic. Transfused and vaso-constrictors. Uræmia three days. Recovered.

		Days after admission.							
	Sp. Gr.	1062	1062	1058					
9.	mm. B. P.	0–70	78	75					
	oz. Urine	0	0	0					
	Sp. Gr.	1066	1062	1056	1056				
10.	mm. B. P.	0–75	95	85–95	82				
	oz. Urine	13	5	12	0				
	Sp. Gr.	1065	1056						
11.	mm. B. P.	100	102	102	100	98	92	75	105
	oz. Urine	0	4	4	14	6	3½	0	0

9. Very severe. Persistent low blood-pressure and fatal suppression of urine in spite of salines.

10. Very severe in opium eater. Fatal uræmia in spite of two transfusions first day and one third day.

11. Mild, admitted third day. Uræmia fatal eleventh day, due to early granular kidney.

CASE 1. *Mild case not requiring transfusion, and recovering without uræmic symptoms.* On the first day the blood-pressure was only 80 mm. and the specific gravity of the blood 1060, and no urine was passed. On the second day the blood-pressure had risen to 106 and the specific gravity had fallen to 1057, and 19 oz. of urine were passed, followed by polyuria, namely 98 oz. the following day and rapid recovery. This is a typical mild case running a favourable course.

CASE 2. *Fairly mild case with high specific gravity and very little urine on the second day. Subcutaneous saline given to dilute the blood, followed by free secretion of urine.* In this instance, although the blood-pressure had risen to 110 on the second day, yet only 1 oz. of urine was passed, which was accounted for by the specific gravity being still 1063. A pint of normal saline was given subcutaneously, and on the following day the specific

gravity had fallen to normal namely, 1055, and 42 oz. of urine were passed, which was increased to 82 the day after, with a good recovery. Here the continued concentration of the blood was at fault, which was remedied by the injection of salt solution into the subcutaneous tissues of the chest and axilla with very satisfactory results.

CASE 3. *Very severe case requiring two intravenous injections on the first day, and subcutaneous injection on the second day for deficient urinary secretion.* This patient on admission had a blood-pressure of 82 and was not collapsed. As, however, I found the specific gravity of his blood registered the very high figure of 1071, which I knew to be a dangerous condition, I had an intravenous injection of three pints given at once. This was fortunate, as in spite of it he collapsed late in the evening and required another transfusion. On the following day he was improving, but the specific gravity was still 1063 and the blood-pressure only 92, so a pint of saline was injected subcutaneously. Up to then no urine had been secreted, but by the evening the blood-pressure had risen to 112 and the specific gravity fallen to 1059, while 13 oz. of urine had been passed. On the third day 60 oz., and on the fourth 106 oz. were measured, an uninterrupted recovery following.

CASE 4. *Extremely severe attack requiring three intravenous injections in the first twenty-four hours. Threatened uræmia on third day averted by a fourth transfusion.* This is one of the most

remarkable recoveries I have seen. He collapsed three times during the first twelve hours in hospital, and received three intravenous injections of hypertonic saline, totaling 12 pints. On the second day he had much improved, and passed 38 oz. of urine, but on the third day his blood-pressure had again fallen to 95 and he passed only 8 oz., so a fourth intravenous injection of 1½ pints of normal saline was given. On the following morning his blood-pressure had risen to 115 and he passed 38 oz. of urine and a day later no less than 116, he made a good recovery and was able to leave hospital on the eleventh day. Before the last transfusion he was in a restless condition with increased respirations as in commencing uræmia.

CASE 5. *Severe case, given 5 pints saline intravenously on admission. Low blood-pressure and deficient urine on the third day.* This patient passed 56 oz. of urine on the second day with a blood-pressure of 102, but on the third day the pressure had fallen again to 92, and only 5 oz. were passed. As he was retaining the rectal salines well (half a pint of normal saline being given by the bowel every two hours, until urine is freely excreted, in all cases as a routine measure), he was treated with cardiac tonics and vaso-constrictors, including adrenalin and pituitary extract. On the fourth day his blood-pressure had risen to 108, and 32 oz. of urine were passed, and on the fifth day the pressure was 115, and 122 oz. were excreted, recovery taking place.

CASE 6. *Very severe. Two transfusions first day, and another on the third day for threatening uræmia.* This patient was admitted pulseless, and received 8½ pints of hypertonic saline intravenously on the first day. On the second day he was doing well and passed 40 oz. of urine, but on the morning of the third day his blood-pressure fell again to 88 and the specific gravity rose to 1065, with restlessness and frequent vomiting. A third intravenous injection was therefore given, and by the evening he had passed 26 oz. of urine, followed by 100 the next day, with recovery.

CASE 7. *Severe attack in a boy aged* 11 *years, requiring two transfusions on day of admission. Continued low pressure with uræmic symptoms relieved by two subcutaneous saline injections.* This boy also was admitted pulseless, and was given two intravenous injections the first day. During the next two days the blood-pressure remained between 83 and 85, and only 6 and 11 oz. of urine were passed. A subcutaneous injection of one pint of saline was given on the second and third days, and on the fourth the blood-pressure rose to 95 and 34 oz. of urine were passed, followed by 47 the next day, with recovery.

CASE 8. *Admitted pulseless and with suppression of urine for thirty-eight hours. Marked uræmic symptoms for three days. Recovery.* This patient was admitted thirty-eight hours after the onset of cholera with complete suppression of urine. He was pulseless and 4 pints were transfused. Soon

after admission he developed well-marked uræmic symptoms with deep laboured breathing, which necessitated his being propped up in bed. On the first day he only passed half an ounce of urine and but 6 oz. on the second day, when his blood-pressure was still only 102 mm. Cardiac tonics and vaso-constrictor drugs were continued, and on the fifth day of his illness, and third after admission, the pressure rose to 115 and 40 oz. of urine were passed, followed by 122 on the next day :—the most remarkable recovery from post-choleraic uræmia I have yet seen. In this case the specific gravity had fallen to 1046 on the second day in hospital, so that it would not have been safe to inject further salines for fear of inducing œdema of the lungs, his face already presenting a puffy appearance.

CASE 9. *Severe collapse requiring two transfusions and followed by persistent low pressure and complete suppression of urine, ending fatally.* This patient was admitted pulseless and although tided over prolonged collapse by two large intravenous injections, the blood-pressure remained persistently below 80 mm. in spite of all measures to raise it, including subcutaneous saline, and uræmia proved fatal after three days. This is an example of the fortunately rare extreme vaso-motor paralysis due to an excessive dose of cholera toxins.

CASE 10. *Opium eater admitted pulseless ; transfused twice on first day and again on third day for threatening uræmia without effect.* This was another very severe case with continued vaso-motor

paralysis in which the repetition of transfusion on the third day for continued deficient renal secretion only raised the pressure to 92, and the uræmia ended fatally. It would have been better to have repeated the saline injection on the second day as the specific gravity was up to 1062, and the blood required further dilution to allow of full secretion of urine. The patient was an opium eater, among whom post-choleraic uræmia is many times as frequent as in others, no less than three out of the seven fatal uræmic cases during the last year having been addicted to this drug. This fact strongly supports the view I have advocated, that opium should never be given in fully developed cholera.

CASE 11. *Admitted third day of mild attack. Late fatal uræmia associated with early granular kidneys.* This woman was admitted late with a blood-pressure of 100 mm. and apparently a very mild case not requiring transfusion. She said she was passing urine with her stools, and it was not until four days after admission that uræmic breathing began to appear, the blood-pressure having now fallen below 100 mm. Drug treatment failed to get the kidneys to act, and on the eighth day after admission Major Stevens, I.M.S., at my request, decapsulated and incised one kidney. She rallied well from the operation, but a few hours later her heart gave out and she died without having passed any urine. Sections of the kidneys showed well-marked early cirrhosis, which accounted for the failure of secretion in spite of

a blood-pressure over 100 in a woman. With my present knowledge the high specific gravity of 1065 on admission would have led me to at once inject saline intravenously or subcutaneously with a good probability of saving such a patient.

The above cases have been selected to illustrate the various points which I have learnt from studying the specific gravity and blood-pressure during the reaction stage of cholera. The great help they afforded in the successful treatment of this formidable complication will, I think, be clear. The precise measures to be adopted in any given case will be dealt with under the treatment of this grave complication.

Inflammatory and Gangrenous Sequelæ.

It is not surprising that the prolonged and almost total failure of the circulation through the distal parts of the body during the collapse stage of cholera should sometimes be followed after reaction by congestion and low forms of inflammation, often going on to suppuration or actual sloughing of the tissues. These sequelæ occur in various parts of the body, the following being most frequently met with.

Parotitis. This complication occurs in about one per cent of cases. It may be bilateral, when there is rapid spread to the surrounding tissues of the neck, and it may prove fatal, especially if not very early incised. In less severe cases it only affects the lobule just below and in front of the ear,

forming a localised abscess with sloughy contents, but doing well under ordinary surgical treatment.

Sloughing of the Cornea occurs in the late stages of severe attacks in old or weakly subjects, who have long lain in a semi-conscious state with the eyes half open. It affects the lower segment of the cornea, and according to Goodeve it may readily heal in recovering cases without serious disfigurement. It has become very rare since hypertonic transfusions have been in use.

Gangrene may affect the penis and scrotum, being then usually fatal. It also attacks the nose, mucous membrane of the mouth, fingers, or toes.

Inflammation of the Lungs is a more frequent and important complication of the later stages of cholera. Pneumonia, bronchitis, pleurisy, and œdema of the lungs may all occur. According to Wall, they are much more common in the colder European climates than in India, pneumonia having been met with in no less than 41 per cent of the cases in the 1892 outbreak at Hamburg. In Calcutta I have lost only from 3 to 5 per cent of my cases from these affections, while they have been less frequent since a more airy ward has been available for the treatment of cholera patients than formerly. Pneumonia in particular tends to run a very rapid course, an increase in the rapidity of the respirations leading to the detection of a patch of consolidation one day in a patient who appeared to be almost convalescent, while on the following day it may prove fatal. Recovery, however, not

unfrequently takes place, although it is always a serious complication. In one case empyema, secondary to a single small abscess in the anterior border of a lung, proved fatal. The patient had been transfused a week before, but as no similar complication occurred in over 100 saline injections in the same year, it appears to have been a sequela of the attack of cholera.

Dysentery and Diarrhœa may occasionally follow an attack of cholera. Numerous old writers refer to them as common sequelæ, but this has been much less marked in Calcutta in recent years. Wall states that both are fairly common during the convalescence of severe cases but yield readily to treatment. I have only met with dysenteric symptoms in about one per cent, all having eventually recovered.

Rarer Complications include a form of poly-arthritis mentioned by Wall, and due to inflammatory changes in the ligaments and fibrous tissues, usually attacking several joints. Other rare conditions are meningitis, paraplegia, dementia, abortion, and, according to Wall, a light roseolous or erythematous rash on the shoulders and loins, occurring about the third or fourth day and being of bad prognostic import. Cardiac thrombosis is said to be an occasional cause of sudden death, although, as a rule, in my experience the coagulability of the blood is reduced in severe cholera. Œdema of the legs may occur during convalescence. Persistent asthenia may also carry off old and

weakly patients in spite of every care, all recuperative power being absent, although they may linger on for some days after the acute stages are past.

Diagnosis

In the endemic area, or elsewhere during epidemic prevalence, there is usually little difficulty in the recognition of well-marked cases of cholera. With the mildest forms, however, it is far otherwise, while they are of great practical importance, as they are equally liable to spread the infection and much more liable to be overlooked. The only way in which they can certainly be detected is by the bacteriological methods already described (see p. 64). Clinically the association of watery vomiting free from undigested food, the passage of copious rice-water stools without any tinge of bile, and early complete suppression of urine, with an algid condition and often muscular cramps, are most characteristic of Cholera Asiatica. During the prevalence of the disease it is wise to regard all cases of severe diarrhœa as being possibly the premonitory stage of cholera, as in this early period many believe that astringent treatment may sometimes cut short an attack, while the use of purgatives in an early stage of cholera will certainly materially hasten the occurrence of the dangerous collapse stage (see p. 100). The diseases which are most likely to be taken for cholera are ptomaine poisoning, infantile diarrhœa,

and acute enteritis due to improper diet, the algid form of pernicious malarial fever, arsenical poisoning, and certain very acute bacillary dysenteries. In none of these conditions do the stools present the completely colourless appearance of the typical rice-water evacuations of true cholera, but they commonly retain some tinge of yellow due to the presence of bile. The urine is also less frequently completely suppressed in these conditions. Curiously enough, infantile diarrhœa does not appear to be as common in the tropics as might have been expected from its wide prevalence in Europe during hot summer months, while cholera is fortunately not frequent in young infants, although very deadly when it does attack them.

Ptomaine Poisoning is of great practical importance, for it not rarely occurs on vessels owing to the consumption of tinned foods, when its differentiation from cholera is essential in connexion with quarantine and other port regulations for the prevention of the spread of communicable diseases. The history of several persons who have consumed the same food being attacked simultaneously will point to ptomaine poisoning rather than cholera, especially if the vessel has been for some time away from an infected port. Within the endemic area of cholera, such as Calcutta, a bacteriological examination of the evacuations may be necessary for the differentiation of the two diseases. The presence of bile in the stools throughout in several cases attacked at the same time would be a strong point

against cholera, this actually occurred in five cases of ptomaine poisoning admitted to the European cholera ward in Calcutta several years ago. Moreover, ptomaine poisoning, if not rapidly fatal, is more quickly recovered from than a severe attack of cholera. The blood-changes may also be of some use, for in ptomaine poisoning the evacuations are less copious than in cholera and consequently the specific gravity of the blood shows little change in proportion to the severity of the general symptoms. Further, although leucocytosis may be marked in ptomaine poisoning, I have several times found it to be absent, which is very rarely if ever the case within the first two days of an attack of cholera. Moreover, I have not met with the great decrease of the lymphocytes and increase of the large mononuclears of cholera in ptomaine poisoning cases. The absence of the comma bacillus and the presence of Gaertner's or other pathogenic members of the coli group would finally clear up the diagnosis.

Algid Malaria is fortunately a rare form of the disease, but it is one which may closely simulate cholera, although it is doubtful if it ever produces the typical choleraic rice-watery stools. The history of previous attacks of fever may help here, while an examination of the blood will at once serve to exclude cholera. Thus, when investigating the blood-changes of a series of cholera cases, I met with a marked leucopænia with an increase of both the lymphocytes and large mononuclears as

in malaria. This led me to search for and find malignant tertian parasites, and on the patient being removed from the cholera ward and treated with quinine she made a good recovery from a grave condition.

Acute Bacillary Dysentery sometimes presents copious watery stools with marked collapse and I have known several such cases admitted to the cholera ward. In these cases I have also usually, although not invariably, found an absence of leucocytosis, while the differential count is quite unlike that of cholera, the large mononuclears not being increased. As soon as a stool has been passed, mucus and also often blood may be detected, and the diagnosis of dysentery can be confirmed by bacteriological examination. It is only very acute bacillary dysentery that I have seen mistaken on first admission for cholera, while if collapse is marked and the blood somewhat concentrated, transfusion is indicated, as in the latter disease. A remarkable example was recently met with in the case of a patient admitted pulseless, with a rectal temperature of 106° F., as a case of cholera. He was revived by intravenous saline, given at a temperature of only 86° F., and the hyperpyrexia successfully controlled. Soon after he passed a very loose stool containing mucus, from which a bacillus closely allied to Shiga's organism was isolated in large numbers. After the saline injection he was still exceedingly ill, but, the nature of the disease being recognized, copious permanganate

injections were administered by the bowel to destroy the toxins in the large intestine and he recovered in a remarkable manner.

Arsenical Poisoning has also to be borne in mind, especially in India, where it is by far the most popular drug in the hands of criminals, and produces violent vomiting and watery purging. The acuteness of the gastric symptoms and the severe abdominal pain will here be the most distinguishing features, although the latter may also be present in certain very acute choleraic attacks. I had hoped that the blood-changes would easily separate the two diseases, but an examination in several cases of arsenical poisoning showed a very marked leucocytosis, as in severe cases of cholera. However, as shown in Table IX, p. 143, the leucocyte formula is of a polynuclear type in arsenical poisoning, both the lymphocytes and large mononuclears being low.

Moribund patients dying of various diseases are also liable to be admitted to a cholera ward on account of their collapsed condition on being brought to hospital, often unaccompanied by any one who can give an account of their illness. Before transfusing such patients for the collapse it is always advisable to take the specific gravity of the blood, for if this is low it is clear that their condition is not due to great loss of fluid from the circulation as in cholera, and intravenous injections, especially if copious, may only hasten death by inducing œdema of the lungs. A good example

of the necessity for this precaution occurred recently. A woman was admitted in a collapsed condition into the cholera ward. As the specific gravity of her blood was only 1048, while very severe epigastric pain was present, although she was very collapsed and obviously dying, I refrained from transfusing, suspecting arsenical poisoning. The case ended fatally in a short time, and post-mortem a hæmopericardium due to ulcerative perforation of the first part of the aorta was found; a condition in which death could only have been hastened by intravenous saline. Another moribund patient admitted as having cholera proved post-mortem to be a case of pneumococcal lobar pneumonia.

Prognosis

Annesley stated that absence of the pulse at the wrist, cold tongue and mouth, very slow and oppressed, or quick and laboured breathing and restlessness, are all bad prognostic signs. Goodeve held that the absence of pulse in the brachial artery, and manifestly impeded pulmonary circulation with dusky livid countenance, are seldom if ever recovered from. These statements remained true until very recently, as up to 1905 in Calcutta there is evidence to show that less than 10 per cent of cholera patients passing into the collapse stage recovered from the disease. Fortunately, with the treatment described later, cases showing all the above signs frequently recover. Thus the

last complete year's records of over 100 cases gave 68 per cent of recoveries among patients in a collapse requiring intravenous salines, and no less than 58 per cent among those admitted with absolutely no pulse at the wrist. Nevertheless, the conditions described above indicate very severe attacks of cholera, in which the prognosis is exceedingly grave unless prompt and efficient treatment is available.

With the present treatment the following are the most important points in the prognosis. Firstly, the age of the patient exerts a marked influence, as already shown in Table V, p. 87, although even over the age of 50 years half the patients have recently been saved, against only 26 per cent formerly. The degree of concentration of the blood before the patient comes under treatment is the most essential element in the prognosis, for if about two-thirds or more of the fluid has been lost from the blood, as indicated by a very high specific gravity, the chances of saving the patient are much reduced, although a number of cases in which this figure exceeded 1070 have recovered. A diminution of the percentage of chlorides in the serum is also an unfavourable sign, as well as a loss of coagulability of the blood with markedly hæmorrhagic stools. Severe abdominal pain and great restlessness and cyanosis are always very serious symptoms in the collapse stage. Lastly, a rectal temperature of over 102° F. during collapse is of serious import, as it is liable to be followed by

a very severe reaction, sometimes passing into fatal hyperpyrexia, which may rapidly ensue on intravenous injections if the danger is not foreseen and guarded against.

After the reaction has been safely surmounted, the prognosis depends almost entirely on the rapidity with which the free action of the kidneys is re-established, this in turn depends on the blood-pressure. If the latter remains permanently below 95 mm. in an adult male, and is accompanied by little or no urinary secretion, the danger of fatal uræmia is very great. A persistent vasomotor paralysis is thus the worst of all signs, as has already been shown in the description of the reaction stage (see p. 103). In the rare cases in which suppression of urine continues in spite of a blood-pressure of 110 mm. or more, the outlook is also grave, as there is generally either old organic disease of the kidney present or the patient is an opium-eater. Lastly, the supervention of late inflammatory conditions, such as pneumonia, gravely enhances the risk of a fatal issue.

Mortality

In the great Bengal epidemic of 1817–23 the mortality of cholera was estimated by different observers at rates varying from 6 to 70 per cent, the diagnosis having then been often very inaccurate, as pointed out by later writers. Jameson, in his report, gave the death-rate in untreated cases as 50 to 70 per cent. Corbyn agreed with this

estimate, but claimed that under the treatment he advocated (see p. 160) only from one-third to one-fifth died, but he received no support from later writers for his sanguine views. Morehead, in 1860, gave the following approximate estimates of the mortality under different conditions. For native troops, coming early under treatment 30 to 45 per cent; in European general hospitals, 50 to 55 per cent; and in hospitals for large civil native populations, such as the J. J. Hospital in Bombay, 60 to 65 per cent. This last figure agrees closely with the results obtained in the Calcutta native hospitals, namely 59 per cent of deaths in the Medical College and 63 in the Campbell Hospital, during a series of years ending with 1905. The official figures given in the annual reports of the Sanitary Commissioner for the Government of India in the decade ending 1908, show a mortality of 78·5 per cent among British troops, 54·2 per cent in native troops, and 62·3 per cent in the jails. In the Calcutta European Hospital from 1895 to 1907 the mortality was 81·6 per cent. It is clear from these data that up to a very recent time there had been no reduction in the mortality of cholera in India since Morehead wrote in 1860.

During epidemics of cholera it is well known that the mortality is excessively high at the beginning and progressively decreases throughout its course. For example, Macpherson records an outbreak at Karachi in which the mortality among the first hundred cases was 79, in the second 66, in

the third 50, and in the fourth only 40 per cent, or but one-half of that of the first attacked. If this is not carefully borne in mind, it is only natural that remedies used in the earlier cases are errone-

TABLE VIII. MONTHLY CHOLERA ADMISSIONS AND MORTALITY

AT THE MEDICAL COLLEGE HOSPITAL, CALCUTTA, 1895–1905.

(Before hypertonic transfusions were begun.)

Month.	*Admissions.*		*Deaths.*		*Recoveries.*	
	Number.	%	*Number.*	%	*Number.*	%
January . . .	90	7·23	64	71·3	26	28·7
February . .	137	11·05	93	67·9	44	32·1
March . . .	217	17·43	139	64·1	78	35·9
April	208	16·71	126	57·8	92	42·2
May	155	12·45	84	54·2	71	44·8
June	70	5·62	34	48·6	35	51·4
July	58	4·66	29	50·0	29	50·0
August . . .	31	2·5	12	38·7	19	61·7
September . .	48	3·86	23	48·0	25	52·0
October . . .	72	5·79	33	45·8	39	54·2
November . .	75	6·02	44	58·7	31	41·3
December . .	72	5·79	52	72·2	20	37·8
1st Quarter . .	444	35·7	296	66·7	148	33·7
2nd Quarter .	443	35·6	244	55·1	199	44·9
3rd Quarter . .	137	11·9	64	46·7	73	53·3
4th Quarter . .	219	17·6	129	58·8	90	41·2
Total .	1,243	—	733	59·0	510	41·2

ously condemned as useless and those administered towards the end of the outbreak are undeservedly lauded as having greatly reduced the mortality of the disease. This fact largely accounts for the multitude of valueless drugs which have been warmly advocated in the treatment of cholera,

and necessitates that any new treatment should be either used in every other case, so as to have an equal number of controls, or continued for many months in a place where the mortality is well known and fairly constant from year to year, as in Calcutta (see Table VIII, p. 136).

CHAPTER V

MORBID ANATOMY AND PATHOLOGY

Post-Mortem Appearances. The body is usually well nourished, a considerable proportion of young muscular male subjects in the Calcutta post-mortem room having, until recently, been victims of cholera. If death has occurred in the collapse stage, the eyes are sunken and rigor mortis is usually strongly marked. The serous cavities are free from the usual small quantity of clear fluid, and are sticky to the touch, this being especially marked on the peritoneal coat of the small intestine. Petechial hæmorrhages are common on the visceral pericardium, especially over the auricles. The auricles of the heart contain only a small quantity of thick dark blood, while the ventricles are contracted and empty. The lungs are lighter in weight than normal, and may appear dry, while the vessels, especially at the bases, contain thick tarry-looking blood. The spleen and liver are congested with similar dark blood, the whole of the portal system of vessels being hyperæmic. The gall bladder is nearly always distended with thick dark-green bile, which can only be forced into the duodenum by the exertion of considerable force, as was first pointed out by Annesley in 1825. The obstruction

to the flow of bile is evidently due to the congestion of the mucous membrane at the entrance of the bile-duct into the bowel. The changes in the stomach are very variable, ranging from extreme congestion with numerous petechial hæmorrhages and a thick coating of mucus in the most marked cases, down to normal appearance to the naked eye. The same remark applies to the internal lining of the small intestine, although it is rarer here to meet with only slight congestion, while the duodenum and jejunum are more affected than the ileum. The latter frequently shows enlargement of the solitary follicles, which stand out as minute seed-like projections on the mucous membrane, but this change may also be absent. The large intestine as a rule shows little or no change, but it may be slightly congested, especially in the upper part. Occasionally in cases with hæmorrhagic stools during life, extensive ecchymoses of the mucous membrane may be found, chiefly in the cæcum. The intestinal contents will be free from bile if the patient has died in the earlier acute stages of cholera, milky fluid containing extensive white epithelial flakes of the mucous membrane being present. The external coat of the small bowel will be more or less congested, often markedly so, and has a sticky feel. The spleen, in addition to being much congested with thick dark blood, occasionally also shows enlargement of the lymphoid tissue of the Malpighian bodies to such an extent as to make them visible to the naked eye

as lighter points, the change being similar in nature to that of the solitary intestinal glands. The lymphoid follicles at the back of the tongue and in the pharynx may also be enlarged and prominent. All these changes appear to be associated with the great decrease in the proportion of the lymphocytes in the blood in cholera, to which I have drawn attention.

The Kidneys. The frequency of fatal suppression of urine after cholera has led to careful investigations of the renal changes. It is commonly held that the epithelial structures are seriously damaged by the toxins of the disease and in fatal cases fail to recover their functions. I have carefully studied the naked-eye and microscopical changes of the kidneys in fatal cholera cases for some years past, and find them to be very variable. Thus, in cases dying in the acute stage nothing beyond congestion of the organs may be found, while microscopically the renal epithelium may be quite healthy in appearance. In patients dying of late complications other than uræmia the kidneys are also commonly normal in appearance. On the other hand, after suppression of urine, the most striking feature has usually been extensive hæmorrhages into the tissues of the organ, especially in the cortex both in the glomeruli and the intertubular tissues. This causes the swollen organ to be tightly compressed by the tense capsule and accounts for the difficulty of perfusing fluid through the organ after death, as already explained (see p. 115). In some of these cases the epithelium of the convo-

luted tubes also showed some cloudy swelling and granular degeneration, but these changes were by no means constant and were sometimes altogether absent in spite of fatal uræmia having ensued. These facts, together with the success which has attended the use of methods to raise the blood-pressure in the prevention and cure of post-choleraic uræmia, make me think that the trouble is more mechanical than due to direct action of the toxins on the renal epithelium. I have also noticed that uræmia is more frequent in the hæmorrhagic form of cholera than in other cases, which is also accounted for by the action of the hæmorrhages into the kidney substance above described.

Early degrees of cirrhosis of the kidney are more frequently met with in the subjects of cholera than in the general run of post-mortems, because, if even a slight degree of this change is present, the chances of recovery from cholera are greatly reduced on account of the difficulty in the excretion of toxins by the damaged renal tissues.

The Blood-Changes in Cholera.

The very great loss of fluid from the body must necessarily produce marked changes in the composition of the blood and it is surprising that these have not long ago been more closely investigated. During the last eight years I have made many observations on this subject, and these have furnished me with data which have a most important practical bearing on the treatment of cholera,

forming, indeed, the key to a system which has very greatly decreased the death-rate from this formidable disease; they are therefore worthy of full consideration here.

The **Red Corpuscles** per cubic millimetre are naturally greatly increased as a consequence of the abstraction of fluid from the blood. In the acute stages they usually number from 6,000,000 to 8,000,000 per cubic millimetre, although they may occasionally even exceed the latter figure. They are highest, as a rule, in cases proving fatal in the collapse stage, but often also greatly exceed the normal in those dying with uræmic symptoms several days after admission, showing that the blood may still remain concentrated during this complication. Table IX shows the average of a number of counts, arranged according to the day of the disease and also divided into fatal and recovering cases, examined during the first three days of the disease. The decline in the count after the fourth day is noteworthy, the lost fluid having been largely replaced by this time. On the whole there is not a sufficiently constant relationship between the number of the red corpuscles and the death-rate to make such a count of much prognostic value, for although all the cases showing over 7,500,000 red corpuscles proved fatal, on the other hand, some with much lower counts died of the disease. All that can be said is that a very high count is a bad sign as indicating excessive loss of fluid from the blood.

TABLE IX. CORPUSCULAR CHANGES IN THE BLOOD IN CHOLERA.

	(1) *Hæmoglobin.*	(2) *Red Corpuscles.*	(3) *White Corpuscles.*	(4) *Ratio of White to Red.*	(5) *Polynuclears.*	(6) *Lymphocytes.*	(7) *Large Mononuclears.*	(8) *Eosinophiles.*	(9) *Large-Mononuclears per Cubic Millimetre.*
(Normal) . .	70	5,000,000	7,500	1–666	68·0	25·0	6·0	1·0	450
1st day . . .	110	6,753,000	32,700	1–233	78·9	7·4	13·0	0·6	4,302
2nd day . . .	104	6,106,000	25,600	1–286	81·8	8·0	10·0	0·2	2,465
3rd day . . .	102	6,486,000	27,350	1–243	74·6	9·5	13·5	0·3	3,713
Later period .	94	5,745,000	18,400	1–628	76·6	10·7	12·2	0·5	1,522
Died, 1–3 days	104	6,238,000	28,800	1–234	78·0	8·3	12·6	0·4	3,671
Recovered . .	108	6,293,000	27,300	1–318	81·1	8·1	10·3	0·4	2·794
Arsenical poisoning (1)	—	6,370,000	24,500	1–260	86·4	8·6	4·2	0·8	1,029
Arsenical poisoning (2)	—	4,770,000	18,500	1–357	89·4	7·0	3·6	0·0	666

White Corpuscles. It is well known that leucocytosis is a marked feature in cholera, and a high degree has been found by Biernocke to be of bad prognostic indication. I have always found leucocytosis present in the acute stages of the disease, and usually also to a less degree in the later ones, as shown in column 3 of Table IX. There was no marked difference in the average number of white corpuscles in the fatal and recovering cases, while of the three highest counts in my series, two with 53,250 and 43,000 respectively got well, and this too although transfusions were not being carried out at the time these counts were made. Still, of nine cases with under 20,000 leucocytes, five recovered, while of fourteen with over 20,000, no less than eleven died, showing a general relationship to obtain between a high leucocytosis and mortality, although a very high count is not necessarily a fatal sign, as Biernocke stated.

The differential leucocyte count in cholera presents very interesting and important features. The counts were made in accordance with the method described in my book on '*Fevers in the Tropics*', all mononuclear leucocytes as large as or larger than the average polynuclear being counted as large mononuclears, so that some which would be classed by others as large lymphocytes are included under the heading of large mononuclears. The advantage of this simple classification is that the count can be very rapidly done with a sixth to eighth-inch objective, and thus becomes an easy

and short procedure. A glance at the table shows that while the polynuclears are only slightly increased in proportion, the large mononuclears, as above defined, are found in considerably increased percentage. On the other hand, the lymphocytes are remarkably reduced in proportion to the increase in the other two principal forms, so that they number only 7 to 9 per cent during the first three days of the disease, being actually fewer than the large mononuclears. This extraordinary deficiency of the lymphocytes is doubtless related to the great increase of the lymphoid tissue in the mucous membrane of the small intestine, and in the spleen mentioned already in dealing with pathological anatomy.

The increase in the total leucocytes, combined with the high percentage of the large mononuclears, produces an extraordinary number of large mononuclears per cubic millimetre. The figures are given in the last column of the table, and show almost a ten-fold increase in the first day of the disease, and nearly as great a one on the two following days. After the third day they only averaged three times as many as normal. This large mononuclear increase was also much more marked in fatal than in recovering cases during the first three days of the disease, and the mortality is largely in proportion to the degree of the change. Thus, recovery took place in no less than four out of five cases showing under 2,000 large mononuclears per cubic millimetre, while of eighteen

with over that number, fourteen died and only four recovered. Over 10 per cent of large mononuclears and under 10 per cent of lymphocytes are both of bad prognostic significance. This fact points to the peculiar change in the leucocyte formula being of a specific nature and due to the action of the cholera toxins, while it also has considerable diagnostic value, as I have not met with this leucocyte formula in any other disease. For example, in two cases of very acute dysentery admitted as cholera cases, I found leucocytosis of a comparatively slight degree present, but no increase of the proportion of the large mononuclears. In ptomaine poisoning again, leucocytosis is said to occur, but in the few cases I have examined it has usually been absent and when it occurred there was no large mononuclear increase. In a case of the algid form of malaria with acute diarrhœa admitted to the cholera ward, I found a low total count with a marked large mononuclear increase, which led me to suspect malaria and this was confirmed by finding numerous malignant tertian parasites in the blood. The patient was removed from the cholera ward, and recovered under quinine treatment.

Arsenical poisoning is common in India and the symptoms closely resemble those of cholera, so the blood-counts in two fatal cases at the end of Table IX are of interest. They show a marked leucocytosis, as in cholera, but the differential count is quite distinct, the polynuclears being

much increased at the expense of both the large mononuclears and the lymphocytes. There is no change in the eosinophiles in either affection.

Loss of Fluid from the Blood in Cholera. It has been already mentioned that Dr. George Johnson in his advocacy of a purgative treatment of cholera, maintained that there is no relationship between the copiousness of the evacuations and the death-rate in cholera, and he therefore condemned transfusion as useless. Wall, however, rightly pointed out that the effect of any given loss will largely depend on the rapidity with which it takes place, a rapid escape of two or three pints being clearly more injurious than that of as many quarts spread over a much longer period, during which some of the loss may have been made good by absorption of fluid given by the mouth or bowel. It is evidently of vital importance to determine this point correctly, for it is most essential to know how far the collapse is really due to loss of fluid from the body in order to decide if steps should be taken to replace it or not. What we really want to know is the extent of the escape of fluid from the blood and whether there is any definite relationship between this loss and the severity of the disease. In order to answer this vital question, I have estimated the proportions of corpuscles and serum respectively in the blood in the acute stages of cholera by means of the hæmocrite. The blood is either rapidly defibrinated or prevented from clotting by the addition of a small measured

quantity of sodium citrate solution (the amount added being allowed for in the subsequent calculation in the latter method). It is then placed in a graduated capillary tube and centrifuged to separate the corpuscles from the serum, when the percentages of each can be noted. By this simple method I have obtained figures given in Table X,

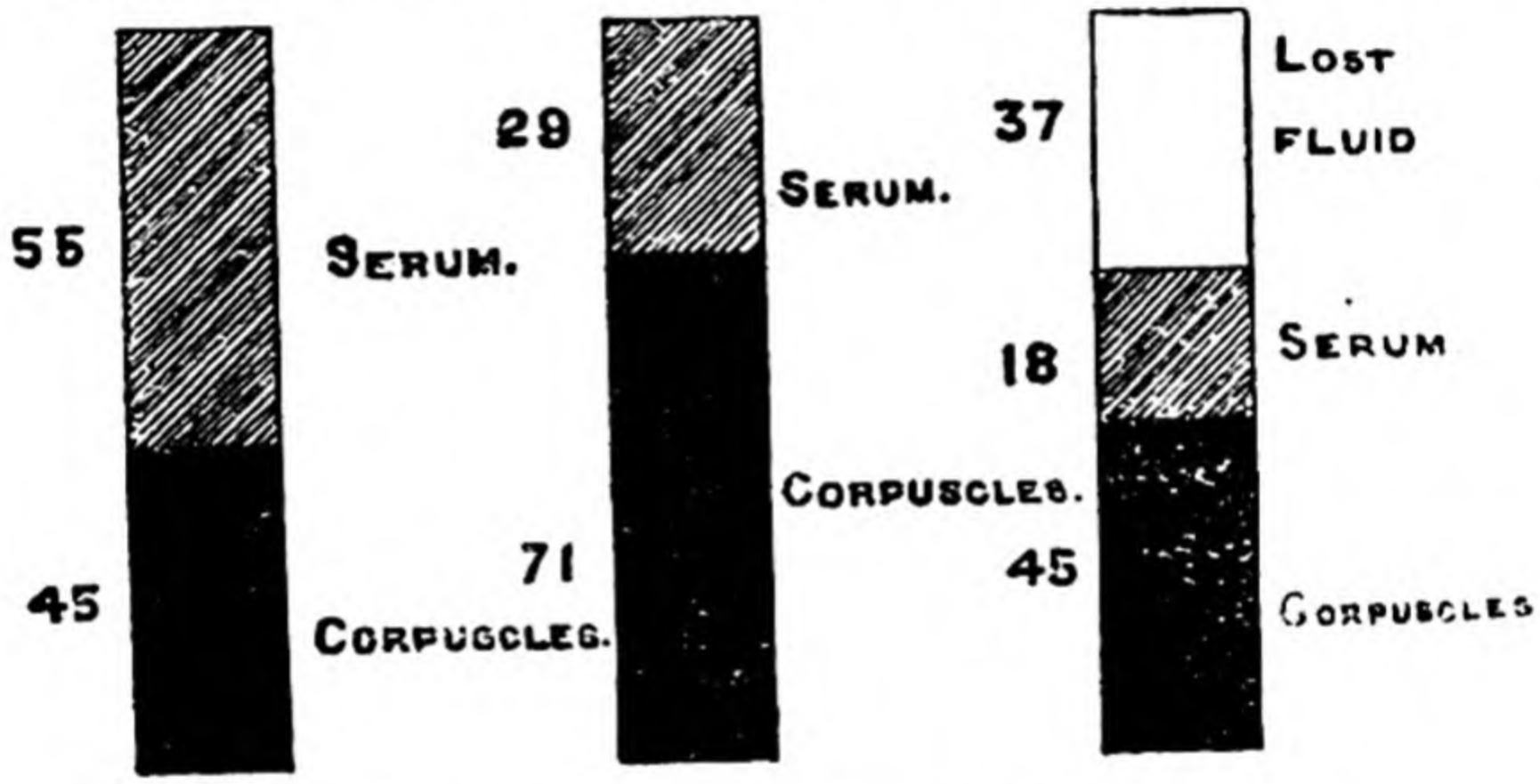
TABLE X. BLOOD-CHANGES IN CHOLERA WITH THE EFFECT OF HYPERTONIC SALINE INJECTIONS.

	Normal.	*Average of 7 fatal cases.*	*Average of 12 cases recovering after transfusion.*	*Average of 5 mild cases not transfused.*
Percentage of corpuscles . .	45	71	63	56
Percentage of serum	55	29	37	44
Loss of fluid from blood . .	—	64%	52%	35%
Pints of saline injected . . .	—	3·7	3·6	—
Serum after transfusion . .	—	61%	61%	—
Blood-pressure before injection	100–110	0–50 mm.	51 mm.	71 mm.
Blood-pressure after injection	—	97 mm.	107 mm.	—
Chlorides before injection . .	0·8	0·79	0·90	0·92
Chlorides after transfusion . .	—	0·95	1·07	—

in which the cases are divided up into three classes, the averages of each being given. The first class includes the most severe type which proved fatal in spite of hypertonic transfusions; the second include cases showing sufficiently severe collapse to necessitate their being transfused; while the third division is comprised of the mild cases in which transfusion was not necessary. It has been already shown that the red corpuscles per cubic millimetre are very greatly increased in cholera, so we may

assume that the diminution of the proportion of serum is due essentially to loss of fluid from the blood and consequently also from the tissues. As the patients were natives of India, in whom the blood normally shows 45 per cent of corpuscles and 55 of serum, we can readily calculate the

DIAGRAM OF CORPUSCLES AND SERUM OF NORMAL AND CHOLERA BLOODS.



CORPUSCLES NORMAL BLOOD. CORPUSCLES CHOLERA BLOOD. COMPOSITION OF CHOLERA BLOOD.

percentage loss of serum in the cholera cases. The figures thus obtained are shown in line 3 of the table. The results are very striking. Thus, in the mildest cases not requiring transfusion, there was a loss of 35 per cent of fluid from the serum of the blood. In the moderately severe cases, requiring transfusion but eventually recovering, there was a loss of 52 per cent; while in the most severe fatal cases the loss was 64 per cent,

or almost two-thirds of the fluid of the blood. The calculation whereby the figures of line 3 of Table X are arrived at can be most easily explained by the Diagram. The first column represents the normal proportions of corpuscles and serum after centrifuging healthy blood in the hæmocrite, namely, 45 per cent corpuscles and 55 per cent serum. Column 2 shows the percentages on centrifuging the blood of a severe case of cholera, giving 71 per cent corpuscles and only 29 of serum. We assume, however, that the corpuscles have not been lost from the blood, so to obtain a diagrammatical representation of the condition of the blood in the cholera case we must reduce the column of corpuscles from 71 to the normal figure of 45, and the serum in the same proportion from 29 to 18, as shown in the third column of the diagram. Thus we find only 18 per cent remaining of the normal percentage of 55 of serum, or a loss of 67 per cent of the fluid portion of the blood.

This method of investigation revealed a most marked relationship between the severity of the disease in its acute phase and the percentage of fluid lost from the blood, while the fact that in all but the mildest forms of cholera from one-half to two-thirds of the fluid had been lost, and presumably a corresponding amount from the tissues of the body, is most striking, clearly indicating the necessity of replacing some at least of the loss if the circulation is to be adequately maintained. This is also borne out by the marvellous immediate

results of saline solutions, which are maintained in the cases in which further copious evacuations do not take place.

Quantity of Fluid necessary to Replace the Loss from the Blood in Cholera. By again measuring the volumes of corpuscles and serum both before and immediately after the rapid intravenous transfusion of given quantities of fluid in cholera, I have also been able to ascertain the quantities ordinarily required to dilute the blood to the normal, or preferably a little beyond that point so as to allow for some further loss of fluid. The saline was run in at the rate of above one pint in five minutes, so the three or four pints usually given were administered within 15 to 20 minutes, which would not allow time for much of it to pass into the tissues before the second estimation was taken. I thus ascertained that three to four pints were required to fully dilute the blood when given at this rapid rate, and in extreme cases even the larger amount occasionally still left the blood more concentrated than normal. Once the pulse has been restored by the injection of about three pints at a rapid rate, then in severe cases another two or three pints can be given at the rate of one ounce a minute without further materially diluting the blood, as it will have time to pass largely into the tissues and thus create a valuable reserve of fluid in the body.

The Specific Gravity of the Blood as a Guide to Transfusion in Cholera. It has long been known

that the specific gravity of the blood rises markedly in cholera, but until recently sufficient use has not been made of this knowledge in the treatment of the disease. The hæmocrite observations above described require a laboratory for carrying them out, but closely parallel results can be much more simply observed at the bedside by taking the specific gravity of the blood and these are accurate enough as a guide to treatment. For this estimation Hammerschlag's benzol and chloroform method is most commonly advised, for which two fluids, a hydrometer and a suitable vessel are all that is required. Chloroform and benzol are mixed in the vessel in such proportions as to make the mixture have a specific gravity of about 1060, and a drop or two of the blood to be tested is placed in the middle of the fluid with a capillary pipette and watched to see if it sinks or falls. If it falls, benzol is added until it rises, and if it floats, chloroform is added until it sinks, the process being repeated until it just floats, when the specific gravity of the mixture will give the required results. According to Da Costa, an ordinary hydrometer gives a reading exceeding the correct figure by from 3° to 10° and he therefore regards this method as both very troublesome and inaccurate for several other reasons. To this objection may be added the offensive smell of benzol. Personally, I have found the following method (first described I believe by Dr. Lloyd-Jones) much simpler and more satisfactory. A number of solutions of glycerine and

water are prepared, preferably at about the mean temperature of the place in which they will be used. Their specific gravities should represent every other degree from 1040 to 1076, a stock solution of each being kept in stoppered bottles. From these a series of small stoppered bottles, holding a few drachms each are filled, duly labelled, and fitted in a small box, the whole being easily made for a few shillings. The estimation can now be rapidly carried out at the bedside by placing a small drop of blood, by means of a capillary tube, in the middle of one of the bottles of glycerine solution of about the specific gravity which is expected to be found. If it rises, it is lighter than the fluid and another drop is placed in a bottle of lower specific gravity, or vice versa, until the one in which it just floats for a second or two is found, or it has been noted to rise slowly in one and sink in the next one, in which case the correct figure will be between those on the two latter bottles. With a very little practice the estimation does not take more than two minutes and it affords invaluable guidance in the treatment of cholera.

In the acute stages of the disease the specific gravity nearly always varies between 1060 and 1072 in natives of India in whom the normal figure in health is about 1054. I have seen it as high as 1076, but only in extremely severe cases. The most common point is about 1063 to 1065, which means a loss of about half the fluid from the blood and is nearly always accompanied by

general symptoms indicating the necessity for transfusion. If the specific gravity is over 1065 it is usually advisable to give an intravenous injection, even when the general condition of the patient does not appear to demand it, as any further loss of fluid is liable to induce sudden and dangerous collapse. Several cases, however, with a specific gravity up to 1065 and a fair blood-pressure of over 70 mm. have made uninterrupted recoveries on rectal salines.

The method of taking the specific gravity of the blood just described is so simple and rapid that it can be repeated towards the end of the transfusion to ascertain whether the blood has been diluted up to or beyond the normal point, being thus of great assistance in deciding how much fluid to run in. If the blood has reached about the normal concentration, but the pulse has not picked up as much as desired, the rate of flow should be greatly reduced to allow time for the additional fluid to pass into the tissues.

Should collapse recur, the degree of concentration of the blood can again be estimated in the same way, and the amount of fluid necessary for an additional transfusion gauged. Once more, after reaction has taken place, if the renal secretion is still deficient, the specific gravity will at once show if the blood is still concentrated and requires additional fluid in the circulation to enable the kidneys to resume their functions. In fact, the estimation is of especial value at this stage, for

the intravenous, or even the subcutaneous, injection of fluid may easily induce dangerous œdema of the lungs, if the blood be already over-diluted; while on the other hand it will commonly at once restore the urinary secretion, if the blood be still concentrated and its specific gravity several degrees above the normal; threatening uræmia has been thus averted in several cases by saline injections in this late stage (see Table VII, p. 117).

The coagulability of the blood is often diminished in cholera, especially in severe and hæmorrhagic cases. I have occasionally found it fail to clot at all in very bad cases. The alkalinity of the blood is said to be diminished in cholera.

The Loss of Salt from the Blood and its Significance. It might naturally be expected that with the great loss of fluid from the blood in cholera the percentage of salts in it would become considerably increased. Edmund Parkes, however, in 1849, showed that the rice-water stools of cholera contained from ½ to 1 per cent of salts, and but very little albumen. I have confirmed this observation, for some estimations I made gave an average of 0·53 per cent of chlorides in rice-watery cholera stools, although there was only a very small amount in the watery evacuations from the stomach. This would mean a loss of half an ounce of chlorides with every 100 ounces of stools. As the chlorides constitute over 80 per cent of the salts of the blood, they may be taken as a guide to the total amount of salts in it at any time. In order to

ascertain the precise effect on the blood of this loss, I have estimated the percentage of chlorides in the serum separated from blood which has been allowed to clot in a number of cases of cholera. The results, including the effect of intravenous transfusions of 120 grains to the pint of sodium chloride (1·35 per cent), are shown in the last two lines of Table X. They are most instructive, for in the most severe fatal class, in which on the average two-thirds of the fluid of the blood had been lost, the chlorides in the serum were slightly lower than normal, instead of being three times as great as would have been the case if no salts had disappeared from the circulation. Moreover, in some of the worst cases the percentage of chlorides was actually below normal, as little as 0·6 per cent having been met with, while the serum showed distinct hæmolysis, which, however, immediately disappeared on the chlorides being raised to a little over the normal point by a hypertonic injection. It is clear from these data that in the most severe cases over two-thirds of the salts of the blood may have been lost from the circulation, and presumably almost as great a proportion from the whole system.

On the other hand, in the recovering cases, the percentage of chlorides was slightly above the normal, although, owing to the great loss of fluid, the total amount of salts in the circulation must have been greatly reduced. Another very significant fact is that when the chlorides in the serum had been

raised to 1·0 per cent or over, death rarely took place in the collapse stage, but in the fatal series this percentage was seldom reached, so that a comparatively high salt content of the blood is of good prognostic significance.

The great practical importance of these observations will be at once apparent. They clearly indicate the necessity for replacing the lost salts as well as the lost fluid, and furnish a complete scientific basis for the use of hypertonic saline transfusions in cholera, which it will be seen from the results recorded in the section on treatment has produced a very remarkable reduction in the death-rate of cholera. The failure in so large a proportion of cases (70 to 86 per cent in different recorded series) of injections of 'normal' saline solutions is now easily understood, for they commonly contained only 60 grains of sodium chloride to the pint, or 0·65 per cent, although we now know that the healthy blood contains 0·85 per cent. In all, except the most severe cases of cholera, the percentage of chlorides in the blood becomes slightly increased, which would have the advantage of tending to retain the remaining fluid in the circulation, and probably accounts for the frequent diminution of the volume of the evacuations once the blood has become concentrated to a certain point. By running in 0·65 per cent saline solution the percentage of salts in the blood would actually be lowered, and the immediate reappearance of the copious evacuations, which nearly always follows

this procedure and leads to rapid recurrence of the collapse, is readily understood. In the worst type, with very low saline content and commencing hæmolysis, normal salines will do nothing to relieve this dangerous condition.

By the use of hypertonic solutions, on the other hand, the saline content of the blood is immediately raised very considerably, with the result that the osmotic currents will tend to carry more fluid into the blood rather than allow it to escape from it, and thus the diarrhœa is checked instead of encouraged, as by normal salt solutions. There is, however, a very definite limit beyond which it is not advisable to go in this direction, for too high a salt content of the blood might possibly give rise to a reabsorption of fluid which has been poured out into the bowel, which may contain a large amount of toxins. The marked temperature reactions following hypertonic solutions may in part be due to this factor, but with due care excessive reaction can almost always be avoided, and if the blood-pressure be fully restored, rapid excretion of the toxins by the kidneys takes place.

CHAPTER VI

TREATMENT

I. Historical

The mortality figures already given prove conclusively that no material advance in the treatment of the disease resulted from the greatly increased knowledge of the causation and pathology of cholera during the latter half of the nineteenth century. The views of the older Anglo-Indian writers on this aspect of the subject are therefore worthy of careful consideration at the present day.

Annesley (1833) used bleeding 'to remove the oppression from the venous system, and to restore the balance of the circulation'. This could only be attained early in the case, before the pulse had been lost at the wrist, that is in comparatively mild cases, for he remarks, 'If blood flows freely, till the colour changes from black to red, the patient will generally recover.' In a later stage the patient often died after 18 to 20 ounces had been removed, but he states, 'in all these cases it will be found that the bleeding ceased after the vessels had been emptied, whether 1 or 20 ounces had been abstracted.' This general use of bleeding in cholera shows what an extraordinary belief physicians of those early days had in this measure

as a universal panacea for all diseases they considered to be of an inflammatory character. Annesley says opium has been recommended, but he is very doubtful if it is beneficial, and latterly he never gave it except in combination with calomel, using 2 grains of opium with 20 grains of calomel, the opium being repeated in an hour if the disease appears to be arrested, and turpentine sinapisms applied to the extremities and body. He also gave cold drinks with dilute nitric acid in them. Green bile-containing stools was a sign that all was safe.

Frederick Corbyn (1832) gave 60 to 150 drops of laudanum, with 15 to 20 grains of calomel as a 'sedative' to stop the violent vomiting and purging, he also advised purgatives such as aloes and jalap. He considered stimulants to be exceedingly injurious and that they materially increased the mortality.

Twining (1833) advised bleeding in the early febrile and inflammatory stages with spasms, warmth, and free circulation, but he recognized clearly the dangers of venesection in the later stages, when it may cause death, and even arteriotomy failed to relieve. He also noted that the blood obtained in this stage gave out no serum. He advised purging with calomel, blue pill, cathartic extract, and castor oil. In some advanced cases he found half a grain of opium every half hour during purging most frequently afforded relief, while in the early stages it may rapidly check the

diarrhœa, but he thought that all the benefit derivable from opium followed quickly after two or three doses, and he warned against overpowering the system in the collapse stage with either opiates or stimulants, ammonia being the best stimulant given in small quantities only. He did not recommend calomel and states that even when taken to salivation it does not prevent the accession of cholera. Contrary to present experience, he found cholera more fatal in natives than in Europeans.

In connexion with the above treatment, it must be remembered that the diagnosis of cholera was very inaccurate in these early days, many simple forms of diarrhœa being commonly included, as is clear from the fact that in some outbreaks the mortality was as low as 6 per cent. It was doubtless especially in cases of purgation due to other causes than cholera that opium so promptly cut short the disease, and thus derived much of its great reputation in the treatment of 'cholera morbus.'

George Johnson (1854–66), during the third and fourth European epidemics of cholera, strenuously advocated the evacuant plan of treatment, and published his views in two little books, the second of which attracted considerable attention. He boldly asserted that there is no relationship between the loss of fluid through vomiting and purging and the severity of the case, and therefore concluded that the collapse and circulatory difficulties could not be due to concentration and

diminution of the quantity of the blood, but he attributed it to a tonic contraction of the small arteries of the lungs producing obstruction of the circulation through them. This arterial spasm he considered to be evidence of the action of a poison circulating in the blood, which must be removed by elimination through the mucous membrane of the alimentary tract by encouraging vomiting and purging, castor oil being the best remedy for this purpose. Saline injections into the blood were quite useless, and could only act by their heat causing relaxation of the arterial spasm. He bitterly complains that the conservative plan of treatment was based on false theories, but makes no attempt to prove the actual existence of the pulmonary arterial obstruction on which his own theory is based, this being still more incredible now that we know that the vessels of the lungs are very badly supplied with vaso-motor nerves. The results of his eliminative treatment in India have been so disastrous as to lead to its complete abandonment. An enthusiastic pupil of Johnson's, Dr. C. N. Macnamara, thus records his experience of it. 'I went boldly to work with castor oil, but it absolutely and completely failed: the mortality from the disease was fearful. I have since, on several occasions, tried castor oil in cholera but I have now finally abandoned it, having never seen any benefit arising from its use.' Now that I have proved that there is a close relationship between the loss of fluid from the blood and the severity

and death-rate of cholera, the essential basis of Johnson's theory is destroyed, and it remains but an interesting page of medical history.

Charles Morehead (Bombay, 1860) advocated one or two full doses of opium, combined with astringents such as acetate of lead, in both the premonitory and evacuant stages of cholera. During collapse no drugs are of use as they cannot be absorbed, so the warmth of the body should be maintained, a little water with an occasional small dose of ammonia or wine administered and frictions applied for cramps. Bleeding and hot baths are injurious. He never tried saline transfusions, as previous experience had been conclusive against their use.

John Macpherson (1866), referring to Johnson's castor-oil treatment, pertinently asks: 'Is, indeed, elimination so defective in cholera that it needs encouragement?' He remarks that the average treatment since 1817 had been wonderfully uniform, with the exception that venesection has been abandoned, and points out that even Sydenham, after commencing with purging, fell back on opium if the disease became alarming. He considered that before collapse had set in opium arrested cholera as certainly as quinine stops malaria. Transfusion had only a temporary good effect, which was not due to its heat, for at blood temperature the results were equally good. Oxygen inhalation was not successful.

Edward Goodeve (Calcutta, 1870) advised that

2 grains of opium should first be given in the evacuation stage. He did not believe that calomel did good, although in 1 to 5 grain doses it did no harm. Next, an astringent mixture of lead acetate and acetic acid was given every half hour, and 1 grain of opium repeated after one hour. No drugs were to be given in the collapse stage, but only cold water or ice to suck, if no vomiting was caused. Ether and ammonia or a little brandy, if there was some pulse remaining. In the reaction stage only a little liquid food is required. 'A little common salt should be added to the food to compensate for the loss of saline matter from the blood.' Do not stop diarrhœa in the uræmic stage, and give lots of water as a diuretic. Regarding the use of saline injections into the veins, he wrote: 'Most of the cases on which the experiments were tried were in a state of extreme collapse, but the recoveries, as shown by Dr. Wright, Dr. Mackintosh, Mr. Twining, and others, do not show that more escaped than might have been expected to, if they had been left to themselves. . . . No means have been found of keeping the injected blood fluid within the vessels: alcohol, laudanum, albumen, and other things have been tried, but have failed, and from this the injection plan has just missed being a great and glorious discovery.'

C. Macnamara (1870) also believed that opium cures the premonitory stage, and thus prevents cholera developing, while he also gave it in the

stage of evacuations, together with dilute sulphuric acid. He considered alcohol 'both theoretically and practically, to be the cause of unmitigated evil'. Chloroform may be given on and off for hours to relieve cramps. No opium must be given during collapse. For suppression of urine he advises cantharides, but received no support for this opinion. He had little experience of saline injections, but thought them worthy of further trial, although too often the fluid rapidly drains away again by the bowel.

A. J. Wall (1893) wrote from a great experience of cholera both in India and in Europe, and well described the methods in general use during recent times. Wall held that the elimination of the poison by purgatives is a purely theoretical line of treatment, which could be proved to be most deadly in practice. Castor oil and calomel he considered to be highly injurious, but even more fatal are saline purgatives. On the other hand, if in the earliest stages the evacuations could be stopped, the course of the disease would be stopped also, for which purpose he advised Tr. opii min. 12 with acid sulph. dil. min. 10, repeated if necessary after two hours. If it was vomited, he injected min. 12 of the liquid extract of opium subcutaneously, observing: 'Opium administered hypodermically before collapse has occurred will, in a large number of cases, save the patient from it, and although the drug is injurious in the later stages of cholera, it is here a choice of evils, and the prevention of the very dangerous

collapse is the most important indication. He considered morphia to be less effective and more dangerous than opium. Once collapse has set in, the time for the use of these drugs is past.

In the collapse stage the condition is critical, and the injection of fluids has to be considered. If there is no pulse and dyspnœa is present, an immediate intravenous injection is necessary. He used 0·4 per cent sodium chloride and 0·2 per cent sodium carbonate dissolved in sterile boiled water, and attributed 'the more favourable results recently obtained by this treatment to careful antiseptic precautions'. He stopped the injection when a pulse of moderate strength had been obtained, 70 ounces being required in severe cases, and in very severe ones as much as 5 pints. In a certain proportion of cases he found this measure to be not only alleviative, but curative. Unfortunately, in the majority in a few hours' time and in some cases even within half an hour, evacuations began again, and the pulse failed once more owing to the injected fluid being lost from the vascular system. It must then be repeated again and again, cases which have relapsed six times having thus been eventually saved, as much as 20 pints having been injected. This measure also afforded great relief and gave time for other treatment. According to Wall, intravenous salines were first used by Latta and Mackintosh in Edinburgh in the first English epidemic of 1831–2, the mortality in 166 operations having been 84 per cent. Wall himself

lost a little over 70 per cent of 193 transfusions. He also found subcutaneous injections of salt solutions over the chest, thighs, abdomen, and arms of great value in cases with a feeble but distinct pulse, a method which has been largely relied on in cholera in India during recent years, having been much more commonly used than intravenous injections.

In the reaction stage he gave copious tannic acid enemata if the diarrhœa persisted, but considered opium to be dangerous at this stage. Intestinal antiseptics, based on Koch's discovery of the comma bacillus, he found to be useless if not actually harmful, as they passed rapidly through the bowel without any effect. He never saw any benefit from calomel, while its after effects may be disastrous, so he advised that it should never be given in cholera, though it is infinitely less injurious than castor oil. Dilute alcohol, in small quantities, he considered to be beneficial, but in large amounts highly injurious. After reaction has set in, beef tea, soups, jellies, and milk may be given. In the uræmic stage, no diuretics should be given, cantharides and turpentine especially being avoided. Mild beverages should be given freely, while warm baths, hot air baths, and dry and wet cuppings are beneficial. The bladder should be watched for suppression of urine.

Kenneth Macleod (1907, *Allbutt's System of Medicine*) practically adopts Wall's treatment as given above. He states that experience has shown that the proportion of recoveries has not been

materially increased by the use of saline injections, and recommends for this purpose 60 grains of sodium chloride and 30 grains of sodium carbonate in one litre (35 oz.) of distilled water, which appears to be a dangerously hypotonic solution, as I find it completely hæmolyses my own blood within three hours in vitro.

Wall's treatment may therefore be taken as that which has been generally followed during the last two decades, although intravenous injections have been much less employed than he advised. As we have seen, the mortality has remained at about 60 per cent for natives in Calcutta, and considerably higher (80 per cent) for Europeans, up to 1907. During the last three years I have been fortunate enough to be able to reduce this death-rate to one-half of the former rate and during the last twelve months to only 23 per cent at the Calcutta Medical College Hospital, by a system of treatment based on my own investigations on the circulatory and blood changes in cholera: a result which justifies me in giving the following full account of the methods I employ in dealing with this formidable disease.

The Author's System of Treatment of Cholera

The observations on the lowered blood-pressure and concentration of the blood in cholera recorded in the previous sections, have placed in our hands the means of obtaining far more accurate

knowledge of the condition of a patient at any given moment and afford invaluable indications for the treatment required. A study of nearly four hundred cases on these lines has led me to the following conclusions regarding the main principles of the treatment of cholera.

1. Whenever collapse occurs (blood-pressure below 70 mm.), replace the lost fluid and salts by a hypertonic saline intravenous injection of sufficient amount to raise the blood-pressure to normal, if possible, so as to ensure a rapid excretion of the toxins through the kidneys.

2. Freely administer by the mouth oxidizing agents to destroy the toxins which are being formed in the gastro-intestinal tract.

3. Carefully watch and control the temperature during the reaction stage.

4. Continue to observe the blood-pressure after reaction, and use all available means to maintain it at a point which will ensure a free excretion of urine.

Although these indications are sufficiently obvious, yet it is only by the most minute and unremitting attention to details that the best possible results can be obtained, as there is no disease in which sudden changes for the worse so frequently occur, requiring both an accurate knowledge of the condition present and prompt application of correct measures to combat them successfully. In the following pages I have endeavoured to fully set forth the treatment I have found best in the

different stages and complications of cholera, in the hope that when combined with a certain amount of clinical experience of the disease, others will be enabled to obtain equally good results as those recently experienced in Calcutta.

I. Stage of Premonitory Diarrhœa

As in this stage the stools still contain bile, it is impossible with certainty to distinguish cholera clinically from other forms of diarrhœa. During outbreaks of cholera cases occur which do not go on to the fully developed disease, but yield to astringent remedies, such as acids and opium, the latter often being given in the form of chlorodyne. Proof is however wanting that attacks apparently cut short by these remedies would have passed on into true Cholera Asiatica if the opium had not been given, as is assumed by nearly all writers on the subject. Similar attacks produced by swallowing cholera cultures in the experiments of Metchnikoff and others nearly all subsided spontaneously, without typical rice-watery stools being passed. For these reasons I am personally rather sceptical regarding the power of opium to cut short a true cholera infection, which would otherwise have passed on into a typical manifestation of the disease. As, however, it is impossible to say, without the delay caused by a bacteriological examination, whether the attack is the premonitory stage of cholera or not, it should be treated with astringent remedies, such as kino and dilute

sulphuric acid. The use of opium requires greater consideration, as it is undoubtedly a very dangerous drug in fully developed cholera. Nevertheless, it frequently appears to cut short severe diarrhœa in the tropics, so a single dose of 20 minims of Tr. Opii or 15 minims of chlorodyne may be given if the stools are still of a fœcal nature, but I never allow this drug once rice-watery evacuations have commenced, and prefer to do without it in any case where a suspicion of cholera exists. The dose should not be repeated, for if collapse quickly ensues, it may remain unabsorbed until the circulation revives in the stage of reaction, which is just the time it is most actively injurious. If there is any reason to suspect the onset of cholera, no purgative should on any account be given, salines being especially dangerous. Rest in bed, avoidance of chills, including those from a punka in tropical climates, and barley water in small quantities at a time to drink are the other indications in the premonitory stage.

II. Stage of Copious Evacuations and Collapse

The great majority of cases of cholera only come under the observation of the physician after very copious diarrhœa and vomiting have occurred, and the patient has already become more or less collapsed, or he becomes so within a few hours after being first seen. Thus, during the last three years in Calcutta, 63 per cent of the cholera cases have required intravenous injections for collapse and in

over four-fifths of these they were admitted to hospital in that condition. Among the remaining 37 per cent who did not pass into the collapse stage, the death-rate was only 3 per cent due to uræmic complications in patients admitted in a late stage, so that the essential problem in dealing with cholera is clearly the treatment of collapse. Any drugs given in this stage with a view to restoring the circulation will be useless, because they cannot be absorbed, while they may accumulate in the bowel and be injurious when the circulation revives. Even drugs of a stimulant or astringent nature, given with a view to acting on the bowel, are largely inert. For example, John Macpherson records a case in which a native swallowed 33 grains of opium and 55 drops of croton oil, yet recovered without a bad symptom and without further purging, while in another instance, 22 grains of extract of belladonna, given by the mouth and rectum, produced no dilatation of the pupils. It is therefore clear that the great problem in cholera is to restore and maintain the circulation and that if this can be successfully accomplished, the toxins will be rapidly excreted through the kidneys and recovery take place without the aid of any drugs whatever. I shall therefore first describe the measures necessary for replacing the fluid and salts which have been lost from the circulation and subsequently return to the consideration of drug treatment.

Methods of Replacing the Lost Fluid and Salts in Cholera

The necessity for restoring the fluid and chlorides lost in the copious evacuations of cholera has already been explained in describing the blood-changes; the manner therefore in which this can be attained may now be considered, beginning with the simplest method, together with the indications for the use of each.

Rectal Injections of Normal Saline Solutions. In comparatively mild cases of cholera the large bowel retains its powers of absorption as long as there is a fair pulse, and the patient may often be tided over the danger of collapse by frequently repeated copious saline enemata. Prolonged observations have shown that if the blood-pressure remains at above 70 mm., rectal injections, if retained, will be absorbed, as shown by a rise in the blood-pressure and a fall in the specific gravity of the blood. Below that point it is not safe to rely on them, as absorption is very deficient and any further copious evacuations will rapidly produce a dangerous degree of collapse. In all cases in which rectal salines are relied on, a very close watch must be kept on the patient and the condition of the pulse; if possible the actual blood-pressure should be noted after any large stool or vomit, in order to immediately detect any fall of the tension below 70 mm., necessitating more active measures. From one-half to one pint should be

given every two hours during the stage of evacuations, this being reduced to every four hours after reaction has taken place, if urine is being passed in good quantity. The injections should be slowly injected as far up as possible with a long soft tube and the patient instructed to retain them as long as he can. In cases in which the blood-pressure is not much over 70 mm., rectal injections may be given with advantage by the slow continued method, the rate being regulated at from a half to one ounce per minute, by means of a stopcock in the course of a tube attached to the graduated bulb shown in Fig. 16, p. 179. The method of regulating the flow is described on p. 194.

For rectal injections I use 90 grains of sodium chloride to one pint, which makes a 0·95 per cent solution, or just about the amount I found in the blood in the milder cases of cholera, as it is doubtful if hypertonic solutions will be absorbed as such through the intestinal mucous membrane. Three grains of calcium chloride to the pint may be added with advantage.

Subcutaneous Saline Injections. The next method to be considered is the subcutaneous injection of saline solutions, which is the one which has been most frequently relied on in the treatment of cholera collapse during recent years in India, having I believe been first extensively employed by Wall. It may be injected into the loose tissues of the chest wall, axilla, or thighs, as is commonly done for surgical shock, one pint

being given at a time and repeated in different parts of the body. If any pulse remains at the wrist it is usually quickly absorbed into the circulation. Normal (or isotonic) solutions have hitherto been generally used for this purpose, but I have found that hypertonic ones are readily absorbed in cholera, and present the same great advantages as when given intravenously.

It may be said at once that subcutaneous injections of salines are very inferior to intravenous ones, while the simplicity of the former is more apparent than real. After a very little experience the intravenous method presents not the slightest difficulty and enables a given quantity of fluid to be administered far more quickly than by subcutaneous injection. The gravest objection to subcutaneous administration is the difficulty of getting in the large amounts required in the collapse of cholera, namely four pints in a case of ordinary severity. These injections cause considerable pain, and may consequently add to the shock the patient is suffering from, while the fluid takes some time to be absorbed when delay may be fatal in a severe case. Moreover, in very marked collapse it may not be absorbed at all, and I have seen a patient die of collapse, with a large amount of fluid in his subcutaneous tissues, which had been injected by a slow continued method but had not entered the circulation. Another serious disadvantage is that owing to the low vitality of the tissues in cholera and the frequent absence of

perfect aseptic conditions in such emergencies, very extensive abscess formation is unavoidable in a certain number of cases, which will greatly retard convalescence, even if it does not turn the scale against the patient. For these reasons, when circumstances permit of the intravenous method, I very rarely employ subcutaneous injections in the collapse stage of cholera and never if it is at all severe. The great advantage of intravenous over subcutaneous salines, even when normal solutions are given, is clear from the results recorded by Nichols and Andrews in the Philippine Islands. Their mortality in cases in which only the subcutaneous method was used amounted to 68·8 per cent, while with intravenous injections it was but 43·6 per cent. Nevertheless, if for any reason intravenous injections are impracticable, frequently repeated subcutaneous salines should be used in all cases in which rectal injections fail to prevent the onset of collapse ; the hypertonic solution recommended later being preferred in the collapse stage, so as to replace the salts as well as the fluid. A sharp slightly curved needle of large bore, attached by rubber tubing to a flask placed at a height of three or four feet above the patient, is used for the subcutaneous injection, both the solution and the apparatus being carefully sterilized by boiling for at least a quarter of an hour.

Intraperitoneal Injections. In order to get over the drawbacks to the subcutaneous method, and to furnish an easier and more rapidly carried out

plan of administering salines in cholera than the intravenous one, I have devised the little instrument shown in Fig. 16, p. 179, to allow of safe intraperitoneal injections. It consists of a steel cannula, the distal end of which is sharpened like a cork borer, while a flange near the other prevents its slipping in too far. A blunt stilette is provided for cleansing and oiling the interior. After carefully disinfecting the skin as for a surgical operation, an incision about half an inch in length is made with a narrow-bladed knife just below the navel in the middle line of the abdomen. This position is chosen because the peritoneum is adherent at the umbilicus, so will not strip in front of the cannula without being perforated. The cut is carried through the subcutaneous tissue and fascia as deeply as is safe. The cannula (without the stilette) is inserted to the bottom of the wound, the abdominal wall is held up on either side by an assistant, and the tube made to penetrate the remaining tissues by a steady boring motion, a finger being placed near the tip to prevent it suddenly slipping forcibly into the peritoneal cavity. By means of a bulb holding sterile salt solution attached by rubber tubing to the cannula, two to three pints in an adult may be rapidly run in from a height of two or three feet, within ten minutes. More than three pints should never be given at one time, although after it has been absorbed the process may readily be repeated through the same incision if necessary. After

withdrawal of the cannula, a deep suture, not penetrating the peritoneum, is inserted, and a small dressing applied with collodion. If any embarrassment of the breathing is produced during the injection, the process should be stopped, while care should be taken not to distend the abdomen or leave the fluid under marked pressure in the cavity. In children not more than one pint should be given at one time. The foot of the bed may be raised to facilitate absorption, as long as this does not interfere with the respiration.

If any pulse remains at the wrist, the fluid is usually rapidly absorbed, with a resulting rise in the blood-pressure and fall in the specific gravity of the blood, while the early re-establishment of the renal secretion may also ensue. Favourable reports of the trials of this method have reached me from several sources, but I have only occasionally used it myself, chiefly in children in whom it may be difficult to find a large enough vein for intravenous transfusion with the cannulae usually supplied for this purpose. Although somewhat more rapid and easy to carry out, I regard it as altogether inferior to the intravenous method, and only recommend it when for any reason the latter is not practicable—which is rarely the case; moreover very strict antiseptic precautions are essential in its use. In one child, signs of slight peritonitis with fever ensued, but complete recovery followed the application of fomentations. When a large number of cases have to be treated with an inadequate

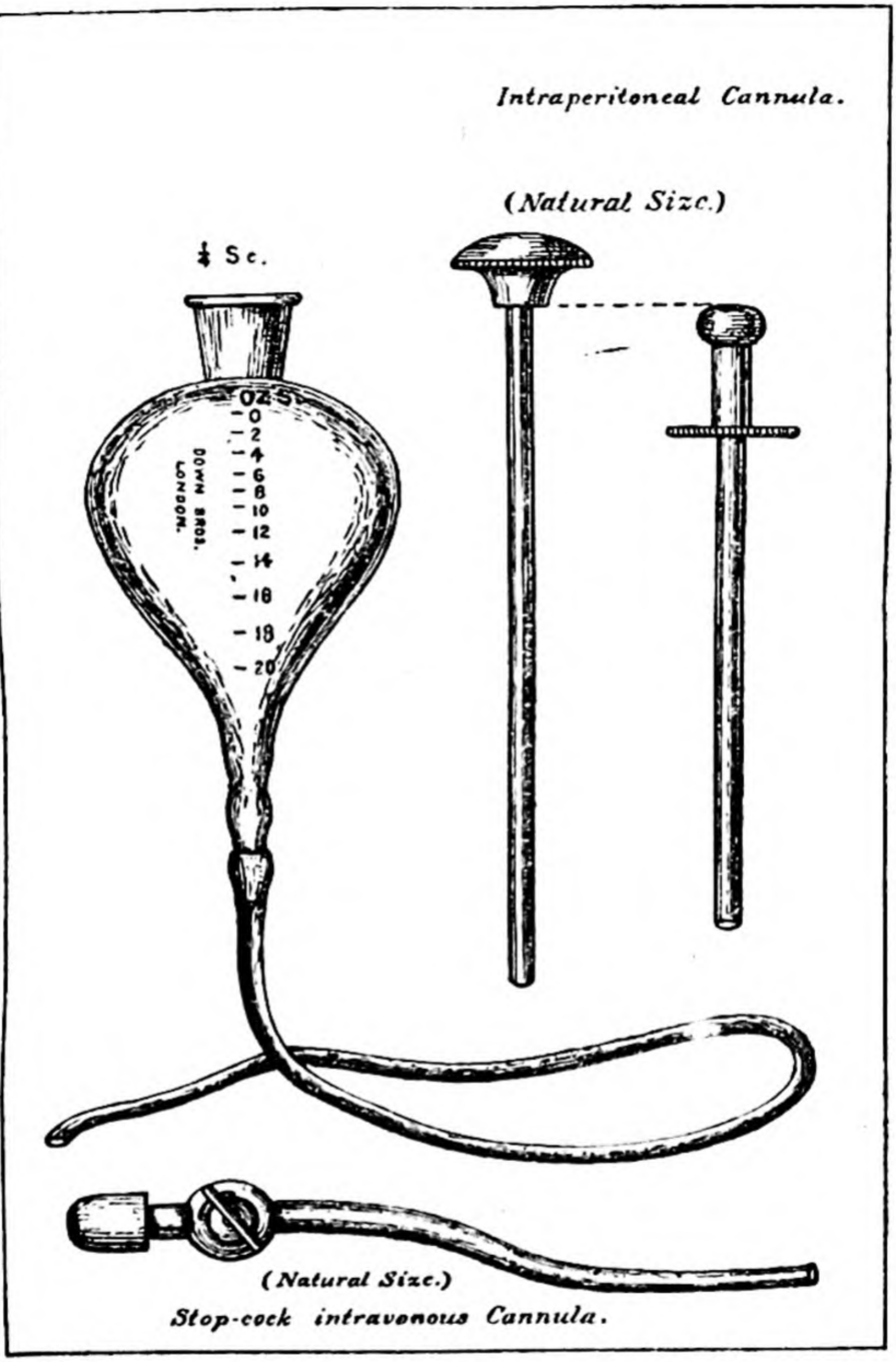


FIG. 16. Instruments for intravenous injections.

staff, time may be saved by using the intraperitoneal method in the slighter degrees of collapse, reserving intravenous transfusions for the more severe ones. Hypertonic solutions should be used intraperitoneally.

A. Powell reported in the *Indian Medical Gazette* of May, 1894, the use of intraperitoneal saline injections in the treatment of cholera, by means of a sharp aspirator needle plunged into the abdomen, and states that no harm resulted, the bowel never being found perforated post-mortem. He recorded temporary improvement in many ultimately unsuccessful cases, but only one recovery. He does not appear to have been followed in this heroic measure.

Intravenous Injections in Cholera. In the history of the treatment of cholera already given, the comparative failure of intravenous injections of normal salt solutions has been briefly recorded, Wall alone was enthusiastic over their use, and yet he admitted over 70 per cent of fatalities following them. Believing that better results might possibly be obtained by regulating the frequency and quantities of the transfusions by estimations of the blood-pressure and the specific gravity of the blood, in 1906, with the help of Captain J. W. D. Megaw, I.M.S., repeated copious intravenous saline injections were used of the strength usually recommended up to that time, namely one drachm of sodium chloride to a pint. We obtained the same remarkable temporary improvement which was previously observed, but the ultimate result on

the mortality was very slight, the case-mortality that year being 51 per cent against 59 per cent in the previous eleven years at the Calcutta Medical College Hospital. In 1907 this measure was again given up as being of very little use and the mortality that year was 59·5 per cent.

On thinking over the possible causes of the generally admitted failure of isotonic saline injections in cholera, it occurred to me that if the salts of the blood become concentrated as a result of the great loss of fluid, then the injection of the so-called normal saline would once more reduce the proportion of salts in the plasma, which in its turn might restart the outflow through the damaged intestinal mucous membrane; when it had been previously checked by the concentration of the blood. I therefore determined to try the effects of injections of stronger saline solutions to maintain a high salt content of the blood, hoping that they might tend to lessen the loss of fluid from the bowel and so maintain the circulation much more efficiently than by the use of weaker salines. At the same time I carried out the investigations already recorded under blood-changes on the concentration and amount of chlorides in the blood, which furnished an additional reason for the use of hypertonic solutions to replace the large amount of salts lost in the rice-watery stools of cholera. I am greatly indebted to Captain Maxwell Mackenzie, I.M.S., for first testing this plan with me during 1908, with the immediate

result of reducing the death-rate from cholera in a large number of cases to but little more than half the rate of the previous eleven years. As this great improvement has been more than maintained during the two following years, so that at the present time the mortality in nearly 400 cases has been only 30 per cent, there can be no doubt about the immense value of the advance made. The following description of intravenous injections is based on nearly three years' experience of the hypertonic solutions in 240 cases, with 57·5 per cent of recoveries, against under 30 per cent in Wall's normal saline cases. During the last twelve months, with the addition of a simple medicinal treatment described later, no less than 68 per cent of recoveries have been obtained in collapse cases requiring hypertonic transfusions (see Table XI, p. 209). As almost all cases in this last series have been confirmed bacteriologically, there can be no doubt about their having been genuine Asiatic cholera.

The Indications for Intravenous Saline Injections in Cholera. The condition of the pulse affords the simplest indication of the necessity or otherwise for an intravenous saline in cholera. Much more accurate and reliable information, however, can be obtained from taking blood-pressure readings. For this purpose one of the many modifications of the Riva-Rocci mercury sphygmometer is best. That recently devised by Professor Leonard Hill is the most portable and convenient, being

made by Hawksley, of 357 Oxford Street, London, W., at £1 5*s*. The same makers supply a still more handy portable sphygmometer at Sir Lauder Brunton's suggestion, in which the pressure is recorded by a needle moving on a small dial, each instrument being graduated with a mercurial manometer. I used one on these lines for many months with satisfactory results, and it will go into a coat-pocket readily. It costs £2 15*s*., with the broad armlet and tubing complete. In using either of these instruments the armlet is strapped round the upper arm and air pumped into the rubber bag contained in it, until the pulse at the wrist is obliterated, the pressure being recorded by a manometer connected through a Y tube. A little of the air is then allowed to escape until the pulse once more returns, and the process repeated until the point at which the pulse is just lost is found, this giving the required information.

As a result of prolonged experience I have come to regard a blood-pressure of below 70 mm. as an indication of the presence of a dangerous degree of collapse necessitating an intravenous saline injection. The simple fact that during the last two years, during which accurate blood-pressure observations have been kept in every case, no patient whose pressure remained throughout at over 70 mm. has died in the collapse stage, is convincing evidence that this is a safe limit to adopt. On the other hand, I have several times had occasion to regret having postponed transfusion

in cases with a pressure a little below 70 mm. on account of their general condition appearing to be fairly good. A blood-pressure below 70 mm. means a very feeble pulse at the wrist, while above that point the pulse is generally a fairly full but still very soft one. Experience has convinced me that the finger is a very fallacious guide in estimating the exact arterial pressure in such degrees of collapse as are indicated by about 70 mm., and even with my present experience I should be greatly handicapped in borderland cases without the aid of the sphygmometer, I would therefore urge its regular use in cholera wards.

Further, very valuable information may be obtained from an estimation of the specific gravity of the blood by the simple means described on page 153. The degree of its concentration is thus at once ascertained. If the specific gravity is raised to over 1060, in addition to the blood-pressure being low, then a copious intravenous saline can be safely given, for much fluid has evidently been lost from the system. Should the specific gravity be found to be over 1065 it is usually advisable to give an intravenous injection, even if the pressure be a little over 70 mm., for the blood is already dangerously concentrated and a single copious evacuation may sometimes produce rapidly fatal collapse, leaving no time for transfusion. I once met with a specific gravity of even 1071 with a blood-pressure of 82, and at once ordered three pints of saline to be given

intravenously. In spite of this he collapsed later in the day and required a second injection, but he ultimately recovered. If the specific gravity is not above normal and the patient is not an anæmic subject, some disease other than cholera is probably the cause of the collapse (see p. 132).

Restlessness, Cyanosis, and Cramps as indications for Intravenous Injections. Although the digital examination of the pulse is often not a very reliable guide to the necessity for intravenous salines in cholera, yet there are certain other symptoms, which when present in marked degree leave no doubt on the point. The most important, because the earliest of these, is restlessness on the part of the patient. If this is combined with severe and frequently repeated cramps, still more if marked cyanosis of the fingers and even of the lips is present, no time should be lost in restoring the fluid amount of the blood, for these symptoms all clearly indicate a very dangerous failure of the circulation in cholera. If the finger be pricked and a drop of blood squeezed out it will be black and often obviously much thicker in consistency than normal, showing great concentration of the blood. As long as a patient's blood-pressure remains over 70 mm. he is not likely to show restlessness in the evacuations stage, although this is not always the case after reaction. It is for this reason that commencing restlessness in the acute stage of cholera should immediately lead to an examination of the patient's pulse, with a view to transfusion or

a second transfusion if the pressure has fallen below 70 mm. In the absence of a sphygmometer the presence of these symptoms is a sure indication of the urgent necessity of an intravenous injection. The certainty with which the restlessness, cramps and cyanosis are relieved by the first pint or two of solution surely indicates the great need for this soothing measure. In many such cases the complete absence of any pulse at the wrist is also found.

The Technique of Intravenous Injections at Given Rates

The choice of a Vein. Owing to the collapsed condition of the vessels in severe cholera the insertion of a cannula into a vein may present some difficulties to those who have never previously performed the operation. Attention to the following simple points will enable any medical man to carry out the procedure with certainty of success. In all but children under ten one of the veins at the bend of the elbow will suffice for the purpose, as long as the end of the cannula is sufficiently small. The form shown in Fig. 16, p. 179, has been made for me by Down Bros., of 21 St. Thomas's Street, London, and by T. Nundon of Calcutta. The end for insertion into the vein is made to taper so as to readily enter a small vessel, instead of the bulbous end of some patterns. It is also provided with a stopcock, the use of which will appear later. In some persons the veins on the dorsum of the hand are large enough for the purpose, but a sudden

movement is here more likely to displace the cannula. In young children the veins of the arm may be too small even for the tapering cannula to enter, but either the long saphenous in the thigh or a large vein which runs over the front of the internal malleolus of the ankle will suffice for the purpose. If the cannula available will not even enter these, the exposed vein may be punctured with a large hypodermic needle attached to the transfusion apparatus, the bulb being well raised to ensure as rapid an entry of the fluid as possible. A small-calibred cannula can also be easily improvised out of a piece of glass-tubing drawn out to the required size and cut off at a convenient length.

The Insertion of the Cannula. No anæsthetic is needed for this small operation, the patient usually being far too ill to heed much what is being done to him. The front of the elbow or other site chosen having been sterilized as well as circumstances permit, a piece of bandage is tied tightly with a slipknot around the limb above the position so as to distend the veins as far as possible. An incision one inch or more in length is made over the course of the vein, which must be carefully exposed and dissected out from the surrounding structures before being opened. Inadequate performance of this step is the cause of most trouble in the later steps. A double strand of silk is now passed under the vein and the lower, or distal, part tied with one strand, while the other is looped loosely round the upper portion ready to be tightened the moment

the cannula is inserted. The vessel is then opened in the following manner. It will still be distended with blood on account of the ligature round the arm, except in the rare cases in which the circulation through the extremities has almost entirely ceased. The superficial wall is seized with a fine forceps, and an oblique cut sloping upwards and backwards beneath the forceps is made with a pair of scissors through half the circumference of the vessel, thus forming a small flap which is held open by the forceps. The cannula is then passed beneath this flap with the other hand and guided by the undivided deep wall of the vein, it must enter its lumen if it is small enough to do so. After being passed in for about an inch, the remaining ligature is tightened around it. By this method a cannula as large as the vein can be inserted, as the flap gives a counter-pull while the tube is pressed into the lumen of the vessel. A longitudinal incision in the vein is much less effective. The vessel holding the solution having been previously filled and all air carefully excluded from the tubing by allowing a full stream to run through before inserting the cannula, it only remains to remove the bandage round the limb to allow the fluid to pass on into the vein. A piece of sterile gauze should be placed over the wound to protect it from contamination during the injection. The top of the flask should be covered in the same way.

Composition of the Hypertonic Solution. I have successfully used solutions containing from 120 to

150 grains of sodium chloride to the pint, but in view of the large amounts which have to be given, I now advise the following for general adoption in cholera for subcutaneous, intraperitoneal, and intravenous injections:

Sodium chloride	grains	120	(8 grammes).
Calcium chloride	,,	4	(0·25 ,,).
Potassium chloride	,,	6	(0·4 ,,).
Water add		1 pint	(568 c.c.).

The addition of the last two salts furnishes the three chlorides in the same proportion as Ringer's fluid, by means of perfusion with which a mammalian heart can be kept beating for several hours, although with sodium chloride alone it will soon cease to act. Both Messrs. Burroughs and Wellcome and Messrs. Parke, Davis & Co. supply soluble combinations of these salts of such a strength that four of them dissolved in one pint of sterile water (any pure water which has been filtered through cotton wool and boiled for fifteen minutes suffices in an emergency) will make a solution of the above strength. Further, if three of them are dissolved in one pint of water the solution will be suitable for rectal administration, or for the injections recommended by me after the collapse stage is over. Two drachms of sodium chloride alone is also quite satisfactory, and was indeed used in many of the first two years' successful hypertonic transfusions. I have not seen any advantage in using still stronger solutions, while I am inclined to think

that they may produce a more violent reaction, possibly due to temporarily increased absorption of toxins from the bowel. It is convenient to have the calcium and potassium chloride made up in a separate strong solution containing 4 grains of the former and 6 grains of the latter in one drachm, which can be added to each pint of hypertonic sodium chloride.

The Temperature of the Fluid. Owing to the markedly subnormal temperature in the collapse stage of cholera it is generally advised to warm the saline solutions to several degrees above blood heat. Thus, Nichols and Andrews advise that the fluid in the containing bottle should be at 43° C. (109·4° F.), which, allowing for some cooling in the tube, would still be from 4 to 6 degrees F. above blood heat on entering the veins. As I have already pointed out in describing the symptoms of the reaction stage (see p. 103), such a temperature is not safe in India, where the great majority of cholera cases occur at the hot seasons of the year, and dangerous hyperpyrexia is a frequent cause of death during reaction, even when no salines have been given. Especially in very hot damp weather an excessive febrile reaction may follow copious hypertonic intravenous salines, but I have observed that this very rarely occurs except in patients whose rectal temperatures were previously above normal during the collapse, in spite of a subnormal surface temperature in the axilla (see Chart 6, p. 109). In fact, I have more frequently found the rectal

temperature above 98·4° F. than not in the collapse stage of cholera, showing that the low surface temperature is due solely to deficient circulation, which will be removed by infusion of salines at blood heat. I therefore inject the fluid at as nearly as possible the normal body temperature whenever the rectal temperature is 99° F. or over. To allow for cooling during the passage of the fluid through the tubing it may be at 100° F. in the flask unless the temperature of the air is but little below blood heat. In the rare cases in which the rectal temperature is a degree or more below normal the solution should be at a temperature of from 102° to 104° F. at first, being lowered later if the surface heat returns. Cases with a rectal temperature below 97° F. are fortunately rare, as they are extremely critical and in my experience generally terminate fatally.

The greatest importance, however, attaches to the cases in which the rectal temperature is considerably above normal at the time transfusion has to be undertaken for collapse. I have seen it vary between 100° and 105·2° F., the latter very high reading having occurred in an absolutely pulseless patient. Dangerously high febrile reaction is very likely to follow large saline injections in such a condition (see Chart 6, p. 109); yet to withhold them is only to allow the patient to die of collapse. It is in European patients that excessive reaction is most frequently seen, this having been the cause of much of the remaining

mortality since saline transfusions have been revived. Fortunately, the discovery of the frequent association of this grave complication with a high rectal temperature during collapse has suggested a way of preventing it, namely by injecting the fluid at a temperature considerably below blood heat, as well as the use of measures to reduce the temperature during the ensuing reaction. Thus, if the rectal temperature is over 100° F. the solution should be run at several degrees below normal, while if the temperature in the rectum exceeds 102° F. I have recently omitted to warm the solution at all, but gave it at the temperature of the room, which happened to be 86° F. In this way even the patient admitted with a hyperpyrexial rectal temperature of 105·2° F. and an axillary one of 100° F. (see Chart 7, p. 110), successfully revived from extreme collapse by a cool hypertonic intravenous injection and ultimately made a good recovery. It may also be mentioned that an exceedingly acute dysentery case, with complete collapse and a rectal temperature on admission of 106° F., was also saved by the same amount of intravenous saline at a temperature of 86° F.; thus this method promises to be an important addition to therapeutics.

The Quantity of Saline to be Injected. In describing the blood-changes, I have already mentioned that about four pints of fluid are required in an averagely severe collapse stage of cholera in an adult male in order to replace the loss from the circulation and to give a slight excess in order

to allow for some further loss. In very severe cases even larger amounts are sometimes required to dilute the blood down to the normal specific gravity, an estimation of which is a valuable guide to the quantities which should be given. If the specific gravity is over 1063, four pints may always be given in an adult, while if this amount has not diluted the blood at least to the normal point an additional pint may be run in at a slow rate, which will allow time for much of it to pass into the tissues. It is quite safe to lower the specific gravity to 1050, or even a little lower, but a careful watch should be kept for any signs of distress or increased frequency of respiration when giving these large amounts, the injection being at once stopped if these symptoms occur as they may be an indication of embarrassed circulation or commencing œdema of the lungs.

The effect of the injections on the pulse and blood-pressure is also an important aid in the judging of how much fluid is required. It is not sufficient to restore the pulse to the point where a feeble beat is felt at the wrist, for even an apparently very fair impulse will often be found to show a blood-pressure of only about 80 mm. This is certainly sufficient to maintain the circulation for a time, but not high enough to ensure renewed secretion of urine, which is so much to be desired to remove from the blood the toxins already absorbed from the bowel. Moreover, a moderate further loss of fluid in the evacuations

will rapidly reproduce dangerous collapse if the pressure has only been raised to about 80 mm. A normal blood-pressure of about 100 to 110 in natives of India and rather higher in Europeans should be aimed at, which means a full-bounding pulse at the wrist such as will ensure immediate action of the kidneys if it is maintained and also allow for some fall due to continued diarrhœa and vomiting without collapse being at once reproduced. In females about three and a half pints will suffice for this purpose, while in children from ten to fifteen years of age two pints may be given.

The Rate of Injection and a simple Method of Regulating it. When marked collapse is present the saline solution should be first run in quickly to restore the pulse as soon as possible. It may, as a rule, be given at the rate of one pint in five minutes, or four ounces per minute, but a careful watch must be kept for any sign of distress, especially in old people. If severe headache or oppression in the chest with quickened breathing is produced, the rate should be at once much slowed. If a stop-cock cannula is not available this may be done by lowering the height of the vessel containing the fluid to only just above the body of the patient, or by partially clamping the rubber tubing.

In order to be able to run in the fluid at any required rate, I have devised the simple apparatus shown in Fig. 16, p. 179, which has been made for me by Down Bros. The transfusion cannula has a stop-

cock, by means of which the flow through it can be easily regulated. The glass bulb for holding the saline is graduated from above downwards to show every two ounces. To regulate the flow the vessel is filled to the mark *O*, and the quantity running out through the cannula in one minute from the height ordinarily used during transfusion (about 3 feet) is timed. If it is faster than desired the stop-cock is turned partly off and the rate again timed, and so on until the required speed is obtained, which can usually be done by the time about six ounces has escaped. The speed can readily be slowed down to from half to one ounce per minute. In very severe cases of cholera, in which three or four pints of saline given at the rate of four ounces per minute does not suffice to fully restore the pulse and dilute the blood to the normal point, a further pint or two may be given at the rate of a half to one ounce per minute. If the copious evacuations continue and collapse rapidly recurs after the pulse has once more been restored by a second rapid injection, the flow may be continued at a very slow rate for several hours if it appears to be doing good. Slow continued intravenous injections may thus be administered by this simple method without recourse to the elaborate apparatus devised by Dr. Cox of Shanghai for this purpose. With the hypertonic solutions, however, renewed collapse is much less common than with isotonic ones, thus continued injections are rarely required and have not proved successful

in the few very severe cases I have tried them in. Any additional quantities beyond the first four or five pints of the hypertonic solution should be only of the strength of 90 grains of sodium chloride and a corresponding amount of the other two chlorides to one pint.

Dr. Cox's ingenious apparatus includes an automatic regulator of the temperature of the fluid and a Berkefeld filter to sterilize the fluid; by this instrument several patients can be injected simultaneously. He has thus given over fifteen pints at one time and twenty-eight pints in a single patient with ultimate recovery, the fluid running out of the bowel as fast as it is run into the veins. He has reported very favourable results in Chinese patients, although not such good ones in European and Indian races. He keeps the fluid at a temperature of 103° to 104° F. and also applies warmth externally. The injections are begun early, if possible before collapse occurs.

Drs. Nichols and Andrews in Manila used isotonic solutions (0·85 per cent of sodium chloride), injecting on the average 1,500 c.c. (just over two and a half pints) with a total mortality of 43·6 per cent. Their average number of intravenous injections in recovering cases was 1·8 and in fatal ones 2·6, which is much higher than with my hypertonic solutions.

Dr. M. A. Vasseliena, working in Russia during 1909, used intravenous isotonic injections in 129 cholera cases, of which only 50 or 38·7 per cent

recovered. With hypertonic solutions, together with toxin-destroying drugs, during twelve months I have performed 69 intravenous injections in cholera with 68 per cent of recoveries.

Repetition of Intravenous Injections. In a considerable majority of cases a single hypertonic transfusion suffices to tide the patient over the collapse stage, although such a favourable result is comparatively rare after normal salines. Thus, a repetition of the hypertonic saline was only given in 28·2 per cent of my cases. During the first two years of their use only 38 per cent of the cases requiring a second injection recovered, showing their great severity. During the last twelve months, however, with the addition of using oxidizing agents by the mouth, 62·5 per cent of patients who required from two to four intravenous hypertonic transfusions have been saved, including one who received thirteen and a half pints in four operations. A blood-pressure below 70 mm. and restlessness with feeble pulse are the principal indications for another injection.

Fluid by the Mouth. In addition to any of the above measures much fluid may be got into the system by the mouth. It is useless to give large quantities at a time as it will only induce vomiting, but by allowing an ounce or two at a time with short intervals it is surprising how much may be retained and absorbed, greatly to the benefit of the patient. As long as the rectal temperature is not subnormal, ice may be given to suck and may allay the irri-

tability of the stomach. Theoretically it would appear to be sound to add a little sodium chloride to the water, but practically the apparent advantage may be more than counteracted by limiting the amount drunk on account of the salt taste. If for any reason transfusion cannot be carried out, however, I consider such an addition to be worthy of trial in severe cases in which the acuteness of the thirst will ensure its ready acceptance.

Medical Treatment in the Stage of Copious Evacuations and Collapse

So various are the remedies which have been extolled as being of great value in the acute stages of cholera that it is safe to conclude that few if any of them have any specific action at all in the disease. Too often their sponsors have been misled by the apparent success of a new drug in the mild terminal cases of an epidemic, forgetting that at the end of an outbreak the mortality will commonly be but about half that of the earlier cases, even when all have been treated in the same manner. In order to obtain reliable data regarding the value of any remedy in cholera it must either have been used in every other case of the disease through a fairly long series or it must be given for several months in an endemic area under conditions in which the ordinary mortality for each season is known. Moreover, the abolition of absorption from the bowel during collapse must be remembered, and the necessary saline injection

for removing that condition must be used, if a drug is to have any chance of exerting a beneficial action, the control cases being similarly treated. In the absence of such scientific data, safe conclusions cannot be drawn from the earlier records of the treatment of cholera, so I shall first give the conclusions I have arrived at from several years' observations under especially favourable conditions in Calcutta.

Should Opium be given in fully developed Cholera? The use of opium in cholera is the most important and difficult question to satisfactorily answer. In the premonitory stage it is nearly universally advised, while once collapse has set in, and still more during the reaction and later stages, it is just as generally condemned as absolutely injurious. The belief of many of the older writers in opium during the acute stage of copious evacuations is striking, although there were not wanting some who denied its value once rice-watery stools had appeared. Wall, as late as 1893, advised that opium should be given as long as complete collapse was not present and he administered the drug hypodermically if excessive vomiting prevented its being retained in the stomach. If the drug is of such great value as appears from the writings of older Anglo-Indian writers in the stage of copious evacuations, then it should also be effective in checking the diarrhœa and tendency to recurrence of collapse once that condition has been temporarily removed by saline

injections. In order to test the value of opium in the acute stages of cholera, I therefore gave a single hypodermic of morphia or opium, either before collapse had set in whenever possible, or after it had been completely removed by hypertonic salines intravenously. Every other case was so treated, while in the alternate controls the only difference was the omission of the opium or morphia, two series of cases at different seasons of the year, totalling fifty-six, being utilized for the test. The mortality among those receiving the narcotic drug was 39·3 per cent, while among an equal number without it the death-rate was but 25 per cent: a very marked difference in favour of the omission of this powerful medicine. Still more striking and important is the fact that no less than 25 per cent of the opium cases died with uræmic symptoms, against only 3·57 per cent, or one-seventh the number, among the non-opium series, which is in accordance with the frequency of fatal suppression of urine after cholera in opium eaters already mentioned (see p. 123). Further, the drug did not appear to have the slightest effect in checking the evacuations and tendency to pass into collapse either in the cases coming early under treatment before its onset, or in those who had been revived by saline injections.

I am therefore convinced that **Opium in all its forms is absolutely injurious in Cholera once the Typical Colourless Evacuations have set in,** and I now never allow it to be given in my wards in any

stage of undoubted or even of suspected cholera. In fact, so convinced am I of the injurious action of opium in the disease that I look on this fact as an argument in favour of trying its physiological antidote atropine, as suggested by Sir Lauder Brunton, but I have not yet been able to adequately test the latter drug. In one case in which a patient had been overdosed with opium before admission subcutaneous injections of one-hundredth of a grain doses of atropine appeared to do much good and to save the man from fatal kidney failure.

Acids. Dilute acids, both mineral and organic, have been recommended from time to time in the treatment of cholera. Mineral acids were extensively tried in the Hamburg outbreak in 1892, but without success, and Davidson has advised diluted acetic acid. I tried giving dilute hydrochloric acid freely in the form of a weak acid drink in every other of a series of cases, but the results were distinctly less favourable in those receiving the acid, uræmic complications were also more frequent so that I am unable to recommend this treatment.

Intestinal Antiseptics. From a very early date large doses of calomel have been extensively used for cholera in India, while, since the discovery of the comma bacillus by Koch in 1883, innumerable antiseptic remedies have been recommended to destroy or limit the growth of the organisms in the intestines, but none of them have been sufficiently successful to come into general use. During the first year of hypertonic salines in Calcutta the

routine drug treatment was calomel in half-grain doses with an equal quantity of camphor, every quarter of an hour up to four to eight doses, as it had previously been in use and I did not wish to change anything except the addition of the hypertonic salines. In the following year these drugs were omitted and eucalyptus oil was given by another physician without any material change in the results, later still I omitted all drugs with slightly better results than previously. I have therefore seen no beneficial results from drugs given with a view to destroying the cholera organism in the bowel and do not know of any conclusive evidence in favour of such a line of treatment, or indeed of any drugs hitherto successfully used in cholera. I have used ten-grain doses of bismuth salicylate in a number of cases and seen no harm result from it.

The Destruction of the Toxins in the Bowel as a Curative Treatment of Cholera

The failure of intestinal antiseptics hitherto to reduce the mortality of cholera may possibly be explained by the following considerations. We know that the comma bacilli are practically limited to the interior of the bowel and only penetrate slightly into its mucous membrane. When the living organisms are injected subcutaneously they perish locally and only produce a slight toxic effect. The symptoms of the disease are largely due to absorption of the specific toxins

from the intestinal contents. Now the cholera toxins are mainly, if not entirely, intracellular in nature and are only set free from the bodies of the bacilli after their death and disintegration in the alkaline bowel fluids, the rice-watery stools of cholera being distinctly alkaline. This being the case, it is easy to conceive that the extensive destruction of comma bacilli in the bowel by intestinal antiseptics may actually result in the more rapid absorption of the deadly intracellular toxins and so aggravate instead of curing the disease. In this connexion it is worth recalling the observations of Gotschlich and Weitgang that in agar cultures of forty-eight hours' incubation only 7·43 of the cholera spirilla which had been present at the end of the first twenty-four hours' growth are still alive, while after sixty-eight hours only 0·8 per cent have survived. This tendency of the organisms to quickly reach their maximum numbers and then as quickly die out and liberate their endotoxins, best explains the short but sharp nature of an attack of cholera, as pointed out by Strong. It at once becomes clear from these considerations that an effectual cure for cholera—apart from any specific anti-choleraic serum—is most likely to result from some simple method of destroying or rendering harmless the toxins within the bowel itself, thus preventing their absorption in fatal doses. I therefore set to work to find such an agent of a non-poisonous nature.

The Action of Oxidizing Agents in rendering

Bacterial Toxins Innocuous. A consideration of the close chemical and physiological affinities of bacterial toxins and snake poisons led me to test the effects of oxidizing agents on the former. The remarkable power of permanganates in destroying the toxicity of snake venoms was shown by Lacerda as early as 1881 and confirmed by Sir Joseph Fayrer and Sir Lauder Brunton soon after. In 1903 (*Phil. Trans. Roy. Soc.*, 1904, B, vol. cxcvii) I tested the action of permanganate of potash on a number of Indian, African, and American venoms, and found they were all readily destroyed by about their own weight of this chemical. I have recently carried out a series of experiments which demonstrates an equally remarkable action of permanganates in rendering harmless certain powerful bacterial toxins. For example, a quarter of a culture tube of comma bacilli, previously killed by heating to 60° C. for a short time, when injected intravenously into pigeons killed them in from twelve to eighteen hours, although subcutaneously such doses are ineffective. Yet I have been able to inject intravenously three times that amount, previously mixed at blood heat for a short time with three milligrammes of calcium permanganate, without death resulting, although some temporary dyspnœa may result from the effect of the precipitate formed in the mixture. The toxin thus appears to have been destroyed by the oxidizing agent.

The practical question remains as to whether it is possible to administer such drugs in sufficient

quantities to exert the desired effect in the gastro-intestinal tract. In the first place, the alimentary tract in cholera is so completely cleared out of its normal contents that any substance having the power of destroying toxins may readily come into contact with the poisons formed there. Further, bacterial toxins for the most part belong to the class of albumoses and other unstable forms of albumen which are readily acted on by oxidizing agents, while from their great toxicity the actual amount of the poisons in the intestinal tract must be extremely small. That permanganates can exert such an action in the body on much more stable substances than albumoses is clear from their well-known antidotal properties in morphia poisoning. That even in very large quantities they are not actively toxic in themselves will be clear from the following case, for information concerning which I am indebted to Captain J. W. D. Megaw, I.M.S. A young adult male swallowed half an ounce of solid permanganate of potash crystals in an attempt to commit suicide. When he was admitted to hospital it was already too late to wash any of the salt out of the stomach, yet he made an excellent recovery after only a fairly acute pharyngitis and a very mild gastritis. I have given over 50 grains of permanganates by the mouth within twenty-four hours in cholera cases without the slightest harm and intend to use still larger amounts in severe cases in future. The small doses formerly given for amenorrhœa could not be

expected to exert an appreciable action in the desired direction in such a disease as cholera.

The administration of Permanganates in Cholera. These salts are given in two different ways. The simplest plan is to give them in solutions to drink *ad libitum* in the place of water. Owing to the intense thirst in the acute stage of cholera there is no difficulty in getting patients to swallow solutions of a strength of from one to six grains to a pint, while I have known double the latter amount to be readily taken by a European patient in a very severe attack, with ultimate recovery. It is usually advisable to begin with the weaker solution and rapidly push it up to at least six grains in a pint as the patient becomes a little accustomed to the astringent taste. Not more than two or three ounces should be given at one time, to lessen the chances of its being vomited. It is not in itself particularly irritating, while I have even known it allay sickness, doubtless by destroying the toxins in the stomach. The best salt for giving in this way is the permanganate of calcium, as it is less astringent, while its lower valency enables it to exert a more powerful oxidizing action. It is also less likely to irritate the mucous membrane, as the less active calcium hydrate will result from its decomposition instead of potassium hydrate. The drug is so cheap that no difficulty will arise on this account even in Indian hospitals.

The other method of using the drug is to give it in pill form coated so as to pass through the

stomach, but allowing it to dissolve in the alkaline contents of the small intestines, where its action is especially desired. For this purpose either salt may be used, but the potassium one is more conveniently dispensed on account of the markedly hygroscopic nature of the calcium and sodium salts. Where this can be got over the calcium salt is preferable and it has been successfully used in pill form in some European cases. In the Calcutta Medical College Hospital the following formula has been employed :

Potassium permanganate . . grains 2
Kaolin and vaseline *quantum sufficit.*

Coat with salol one part and sandarach varnish five parts, or with keratin.

The pills should readily dissolve in one per cent alkaline fluid at a little below blood heat and produce a deep red solution. It is important to see that pills which have been kept for any time still retain their properties, as if they become hard they may pass through the bowel unchanged and without exerting any action. Messrs. Burroughs & Wellcome supply the above prescription in a convenient form.

The pills are always given in addition to the permanganate drinks in the following manner. Immediately on admission one pill containing two grains of the salt is given every quarter of an hour for two hours and then one pill every half-hour; any pills which are rejected by the stomach are replaced without delay. They are continued until

the stools become green and less copious, this usually occurs in about twelve to twenty-four hours with this treatment. In mild cases it will suffice to continue the pills during each alternate four-hourly period. Barley water may be given in the intervals between or together with the courses of pills, as it is not readily acted on by the permanganates. If nursing arrangements are deficient during an epidemic, two or more pills may be given at a time with longer intervals. At the beginning of the second twenty-four hours, eight more pills (containing 16 grains of permanganate) are given within four hours. In severe cases this is again repeated at the beginning of the third day to prevent a relapse—such actually occurred in three cases, although they all promptly yielded to a repetition of the permanganate treatment, thus furnishing additional evidence of its directly curative action. Nothing but barley water should be given during this treatment, animal foods, such as soups and milk, being absolutely avoided. The above doses of potassium permanganate are what I have so far used, but in very severe cases I intend to double them in future, as I have never seen the faintest indication of harm having resulted from the drug, although I should prefer to use the calcium salt in the pills when many of them are being given.

Results of the Hypertonic Saline and Permanganate Treatment. Table XI shows the case-mortality at the Calcutta Medical College Hospital under different methods of treatment for the last

sixteen years. The first line includes eleven years when rectal and subcutaneous normal saline (one drachm to a pint of sodium chloride) was almost solely relied on. The death-rate during this period averaged 59·0 per cent, and it varied but little from year to year. During the last six of these eleven years the mortality was 61·2 per cent, so there was no evidence of any recent improvement in the results shortly before I commenced my investigations on transfusion in cholera.

TABLE XI. RESULTS OF DIFFERENT FORMS OF TREATMENT OF CHOLERA.

Period.	*Treatment.*	*Cases.*	*Deaths.*	*Percentages.*	
				Deaths.	*Recoveries.*
1895–1905	Rectal and subcutaneous salines	1,243	783	59·0	41·0
1906 . .	Normal salines intravenously	112	57	51·9	49·1
1907 . .	Rectal and subcutaneous salines	158	94	59·5	40·5
1908–1909	Hypertonic intravenous salines	294	96	32·6	67·4
8–09—7–10	Hypertonics plus permanganates	103	24	23·3	76·7

In 1906, when normal salines were used intravenously by Captain Megaw and myself, the rate fell slightly to 51 per cent, but on the intravenous injections being once more given up in 1907 as of little use, it rose again to 59·5 per cent.

The hypertonic solutions were commenced early in 1908, and during two years' observations the mortality among 294 cases was only 32·6 per cent, or but little more than half the previous rate, thus affording conclusive evidence of the great life-saving value of the new method.

Still, a number of very severe cases were lost either from renewed collapse or severe reaction, and I realized that further progress could only be expected from either a specific antitoxin for intravenous injection, or some method of limiting the absorption of the poison from the intestines. For the reasons already explained, I started the permanganate treatment in August, 1909, and by the end of the year had only lost one out of seventeen cases, including ten severe ones which required transfusion. Knowing that such a phenomenal recovery rate could not possibly be maintained during the height of the cholera season in the first five months of the year, I determined to continue for twelve months before fully analysing the results. These are shown in the last line of Table XI, 24 out of 103 cases having been lost, or 23·3 per cent, being a two-and-a-half-fold reduction on the old rate from 1895 to 1905, and 10 per cent lower than that obtained by hypertonic transfusions without the toxin-destroying oxidizing agent. This further gain is particularly satisfactory, as it can only be due to saving very severe and hitherto hopeless cases. As much was learnt during this last year, I still hope for a slight further reduction in the death-rate, although the fact that over one-third of the Medical College Hospital patients are admitted with absolutely no pulse at the wrist precludes the likelihood of more than 80 per cent of recoveries being obtained. It is important to note that during this last year the diagnosis has been confirmed in

almost all the cases by bacteriological examinations, while all clinically doubtful cases were excluded. A large proportion of the comma bacilli isolated from the stools gave the specific serum reactions in high dilutions, such as 1 in 10,000, so there can be no doubt as to the true nature of the disease. In view of the importance of these results, however, it will be well to analyse the cases more fully in order to see if any other factor, such as the prevalence of an unusually mild type of cholera, may in part account for the phenomenally low death-rate.

With regard to the severity of the disease we have an admirable control in the cholera ward of the neighbouring Campbell Hospital, as for a number of years previously to my reviving transfusions at the Medical College the mortality of the two institutions ran closely parallel. During the first three months of 1910 my methods were not used at the Campbell Hospital and their cholera mortality was 71 per cent, the disease having been of at least the average or somewhat over average severity. In the middle of April hypertonic intravenous injections and very weak permanganate drinks were commenced at the Campbell Hospital, and during the next three months the mortality fell to 34 per cent, against 64 in the same months of the preceding year, the Assistant-Surgeons in charge attributing the great improvement to these measures. Another test of the severity of the disease is the proportion of severe cases requiring transfusion. During the last three years, 63 per cent

of the total admissions have had to be transfused, while during the year of permanganate treatment the same figure was 67 per cent, so that the proportion of serious cases was actually higher than in the previous period and the further reduction of the mortality due to the toxin-destroying drug is all the more striking.

A still better test of the effect of any given treatment is to consider only the severe cases requiring transfusion for collapse. In the eighteen months of hypertonic injections without permanganate the recovery rate among 170 operations was 54 per cent, leaving 46 per cent of deaths. Since the addition of the oxidizing drug, 68 per cent of sixty-nine transfusion cases have been saved, leaving only 32 per cent of deaths, although previously to the use of hypertonic solutions certainly under 10 per cent of collapsed cases recovered. As the mortality of the milder cases not passing into collapse is extremely low, not more than 3 per cent recently, it is clear that there has been a seven-fold reduction in the mortality of the severer types of cholera at the Calcutta Medical College Hospital, during the past twelve months, over that of the period before I introduced the methods of treatment here described.

An even more crucial test is obtained by considering the cases which were so severe as to require more than one hypertonic intravenous injection. Before the addition of the permanganates only 38 per cent of fifty such cases were saved, while since the addition of the drug 62·5 per

cent of twenty-four of these extremely serious cases have recovered. Once more, if we take those patients in whom no pulse could be felt at the wrist on admission, or it was too feeble to allow of the blood-pressure being measured there, no less than 58 per cent have been rescued from practically certain death during the last twelve months of the new treatment.

Effect of the Treatment in different Stages of Cholera. If my contention that permanganates actually destroy some of the cholera toxins in the bowel is correct, then the new treatment should have most effect in those cases which come early under observation. In this connexion it must be borne in mind that the ordinary mortality from cholera is highest among those coming into hospital within the first twelve hours of the onset of the disease, and considerably lower among later admissions, as Morehead long ago pointed out. This is simply because the more virulent the disease the more rapidly will serious collapse requiring removal to hospital come on. Table XII illustrates the point.

TABLE XII. RELATION OF PERIOD OF ADMISSION TO DEATH-RATE IN CHOLERA.

Hours after Onset.	*Up to 12 hours.*			12 *to* 24 *hours.*		
	Cases.	*Deaths.*	*Percentage.*	*Cases.*	*Deaths.*	*Percentage.*
Hypertonic salines . .	74	33	44·6	94	19	20·6
Do. (plus permanganates)	46	9	19·6	36	8	22·2

These figures clearly show that the additional gain from the permanganates has been due essentially to the marked reduction of the mortality among the severe cases admitted within the first twelve hours of the onset of the disease, that is, before a fatal dose of toxin is likely to have actually entered the blood from the bowel, which is precisely the time when oxidization of the toxins in the intestines would be most likely to be beneficial.

Finally, if the cholera toxins are rendered harmless to any material extent in the bowel, then a smaller number of patients admitted with a blood-pressure of over 70 mm. should collapse and require transfusion, after having been some hours in hospital, than was the case before the use of the permanganates. An analysis of my cases from this point of view shows that with the hypertonic injections alone 21·5 per cent of the transfusions were required for failure of blood-pressure some time after admission. Since the permanganates have been added, only 12·8 per cent of such cases have occurred, or but little over half as many. Moreover, in nearly all of these latter the collapse has come on within four hours of admission, that is, before the oxidizing agent had time to fully produce its effects.

The foregoing data afford strong support to my contention; again the clinical effects were equally good and were particularly striking in very severe cases requiring two transfusions within a few hours. Formerly, in the unusual event of the recovery of

such patients, they remained in a critical condition with marked toxæmia for several days. On the other hand, with the permanganate treatment I have repeatedly been astonished to find them practically convalescent within twenty-four hours, showing very little signs of the terrible ordeal through which they had just passed. In moderately severe cases admitted in a state of collapse the copious rice-watery stools had changed to small green ones in twelve to twenty-four hours, this was formerly quite uncommon. At the same time, the number of comma bacilli in the stools usually become very greatly reduced. Thus, everything points to the permanganates having a definite curative action in cholera and I have no hesitation in recommending their adoption as a routine treatment in combination with hypertonic salines whenever necessary, as being superior to any other therapeutical measure yet subjected to prolonged and critical trial.

At the same time, I am very far from claiming the new treatment as an infallible remedy for cholera. On the contrary, the more I see of this terrible disease the more fully I realize the impossibility of saving certain extremely virulent forms, especially if they come under treatment late, when a fatal dose of toxin has already been absorbed. Some day a powerful specific serum may be available, meanwhile, I am about to try oxygen inhalations in the hope of destroying part of the toxins in the blood. In any trials of my methods it should be borne in

mind that the mortality at the beginning of an epidemic is much higher than towards the end, or they may be condemned on account of apparent failure in the early and hopelessly severe cases, although if persevered with to the end they can scarcely fail to reduce the total mortality in the same way as that obtained in Calcutta. Due allowance must also be made for the greater mortality in epidemics than among sporadic cases within an endemic area. Lastly, the permanganates alone will be of but little use without the addition of hypertonic salines in those patients who become collapsed.

Results obtained by others with the Hypertonic Salines. The Jaganath festival at Puri in July is always accompanied by an outbreak of cholera, during the seven years up to 1909, during which the pilgrim hospital has been open, the case-mortality has averaged 69·5 per cent. In 1910 the Sanitary Commissioner, Major Clemesha, I.M.S., arranged for an assistant surgeon trained in my ward to be sent to Puri during the festival to carry out my treatment. He worked under the civil surgeon, Dr. Pulipaka, who reported to me that fifty cases of cholera were treated with a death-rate of 23, or 46 per cent. As no nursing could be provided, and half the patients were over 40 years of age, one-third between 50 and 70 years, and nine of the deaths took place within a few hours of admission in a moribund state, in five of whom there was not even time for transfusion to

be attempted, this was a most satisfactory result, which should be improved on in future years with more complete arrangements.

Captain T. C. Rutherford, I.M.S., also reports to me that he has treated thirty-nine cases at Bilaspur, in the Central Provinces, by hypertonic saline injections, all intravenously (except one intraperitoneally in a child, with recovery). He only lost nine, or 23·07 per cent, while the mortality among fifty-nine cases occurring in the same area at the same period of time, but not treated in hospital, was 62·76 per cent. In all the cases the injection, usually of four pints of 120 grains of sodium chloride to the pint, was given immediately on admission irrespective of the condition of the pulse. As these cases occurred outside the typically endemic area where very few mild cases occur and in a district hospital without the staff and facilities of Calcutta hospitals, Captain Rutherford was doubtless right in transfusing every patient on admission. As his results under ordinary district conditions in an epidemic area are fully equal to the best I have obtained in Calcutta, it is evident that my plan of treatment is quite practicable in any Indian hospital, and the simple apparatus required for the intravenous injections can be obtained for Rs. 15 from Bathgate & Co., of Calcutta.

Serum-Therapy. The experimental work leading to the production of antitoxic serums against cholera has already been dealt with (see p. 70).

In practice their efficiency has not yet been fully established, although some favourable results have been reported in a small series of cases. Thus Berdnikoff, using Schurupow's serum, reports a death-rate of 59 per cent among forty-four cases treated with the serum, against 72 per cent of deaths in twenty-five controls. From 30 to 50 c.c. of serum was injected either subcutaneously or intravenously.

Salimbeni has also reported on forty-two cases treated at St. Petersburg, with a mortality of only 23·8 per cent, against a case-mortality in the official returns of 45·6 per cent. Unfortunately, he used in addition to the serum large injections of saline solutions both subcutaneously and intravenously, and much of the relief of the symptoms, which he appears to attribute to the action of the serum, such as the disappearance of cramps, is also always afforded by saline solutions alone. It is thus impossible to say how far the good results obtained were due to the saline injections, and how far to the specific serum. In order to ascertain this it would be advisable to treat every case with hypertonic salines by my method, and in every other case to use in addition the anti-choleraic serum. I have tried to obtain some of the Paris serum for such a test, but was not fortunate enough to receive any answer to my request. Salimbeni used doses of from 100 to 350 c.c., so the treatment is likely to be an expensive one, but it might well turn the scale in very severe cases. It is

much to be desired that the results of critical and properly controlled trials of the serum will soon be available.

Reaction Stage

When the evacuations become reduced in amount and the pulse slowly regains its strength, accompanied by return of warmth to the surface of the body, the reaction stage is entered on, but the danger to the patient is very far from being over. Indeed, many of the Anglo-Indian writers regarded this period as quite as dangerous as the collapse stage. The two great sources of anxiety now are firstly, excessive febrile reaction, and secondly, continued suppression of urine followed by uræmia, in addition to which various inflammatory complications may ensue.

The control of the Febrile Reaction. The frequency of a high rise of temperature, even reaching a hyperpyrexial point, the latter sometimes following on intravenous injections, although also occurring apart from the use of any salines, has already been pointed out (see p. 104). The discovery of the fact that this serious complication is most common in those patients whose rectal temperatures are above normal during collapse, enables the danger to be foreseen and to a large extent prevented by administering the salines required for collapse at a subnormal temperature in such cases. The temperature in the rectum should also be taken every quarter of an hour after

intravenous injections, to enable any tendency to an excessive rise to be detected in time to allow of the following preventive measures being at once adopted. The occurrence of a rigor or restlessness and delirium at this period should also lead to an investigation of the patient's condition, when a burning hot skin will often be found. These symptoms indicate a dangerous degree of fever, which indeed is rarely recovered from if complete unconsciousness ensues.

A copious iced-water rectal saline of not less than one pint should at once be given at as low a temperature as can be quickly obtained. Ice should be applied to the head, and cold sponging continued until the temperature falls. A surface temperature of over 103·5° F., or a rectal one of over 104° are indications for the use of cold sponging and ice to the head, while if it continues to rise the more severe measures of iced-water enemata or a cold bath will be required. As long as the rise of temperature is of short duration and quickly controlled, even a surface temperature of 106° F. may be recovered from, especially if it rapidly follow an intravenous saline.

Another important practical point, which is too often neglected, is that as intravenous injections are always followed by a febrile reaction, it is not only unnecessary but is actively injurious, to surround the patients with hot water bottles during the process. I have several times seen a patient whose temperature was rapidly becoming hyper-

pyrexial during transfusion, who was covered with very hot rubber water bottles, while the increasing restlessness due to the rise of temperature was being looked on as an indication for continued saline injections. Personally, I hold that the external application of warmth to the body, even during the cold collapse stage, is nearly always harmful, except perhaps in the few cases in which the rectal temperature is markedly subnormal. When we bear in mind the great loss of fluid from the body in cholera, it becomes clear that the coldness of the surface and extremities during collapse is very largely a conservative process in order to retain the small remaining supply of blood for the vital internal parts. By drawing the blood to the distal parts the collapsed condition can only be increased. For these reasons I never allow the use of hot water bottles, &c., in my cholera ward, except only where the rectal temperature is subnormal.

Do not check Diarrhœa in the After-stage of Reaction. Astringent remedies have frequently been recommended at this period to finally stop the now greatly diminished diarrhœa. Experience, however, has convinced me that this is wrong, owing to its leading to an increased absorption of toxins through the damaged intestinal mucous membrane. I therefore make no attempt to check the diarrhœa in this stage, but leave the reparatory processes in the bowel entirely to nature. Opium and acetate of lead are particularly deadly as they actively pre-

dispose to fatal uræmia. Acids are not so positively dangerous, but I have seen late fatal febrile reaction follow their use, as if toxic absorption had been increased. The diarrhœa will cease by itself in good time if the diet is properly regulated. As long as rectal salines have to be continued fairly frequent watery, but coloured, stools will be passed, but this is of no consequence and will cease when the salt solutions can be safely omitted on the free secretion of urine being thoroughly established.

Diet. I have already mentioned that only barley water is given during the acute stages of cholera. This should be continued during the reaction, but much caution is necessary in adding to the diet. Too early administration of milk, soups, and jellies, containing animal albumens is particularly likely to be followed by a relapse and it is thus far more dangerous than temporary partial starvation. In severe cases all such animal food should be withheld for two or three days, and farinaceous foods only be given, thin arrowroot or cornflour being first given. When milk is subsequently allowed it may first be given in the form of whey, to avoid the irritant action of curds. When the acute diarrhœa has stopped for two days or more, custards and other light food may be commenced, the diet being gradually increased with the improvement in the general condition and appetite of the patient. Even in mild cases it is safest to err on the side of excessive caution for fear of a relapse. As long as the kidneys are not acting freely, soups

rich in extractives should especially be avoided. It is surprising how rapidly the digestive tract usually resumes its functions after severe cholera, so that with these precautions the diet rarely gives much trouble in the after-treatment of the disease.

Alcohol was nearly universally condemned by the older Anglo-Indian writers as absolutely injurious in cholera, but some more modern authorities considered that small quantities might occasionally be beneficial. In the collapse stage it should certainly be entirely avoided, as tending to increase the shock by inducing vaso-dilatation and determination of the blood to the surface of the body where it is not wanted, while it is useless to stimulate the heart when there is too little fluid in the circulation for it to act on. In the later stages it may occasionally be beneficial in small quantities and in a dilute form, especially in elderly people and those who have long been habituated to its regular use. In native patients I scarcely ever prescribe it.

Ammonia is advised by many writers and I believe it to be of considerable value in the reaction stage, especially if there is any tendency to congestion of the lungs. It may be given in the form of ammonium carbonate and sal-volatile every four hours, to which may be added tincture of nux vomica and five-minim doses of tr. digitalis if the blood-pressure is deficient and the urinary secretion not free.

Measures to ensure Free Action of the Kidneys after Cholera

The second great danger after reaction in cholera is continued deficient action of the kidneys, ending in the deadly post-choleraic uræmia. The dependence of this very serious complication on low blood-pressure and high specific gravity of the blood has already been described and illustrated by a number of cases (see pp. 116–124). Now that this grave danger can be foreseen at an early stage, much can be done to prevent its occurrence by fully diluting the blood and raising the pressure in the circulation sufficiently high to ensure renal secretion; for this purpose the following measures are available.

As already mentioned, the rectal injections of isotonic salines should be regularly continued after collapse is past until at least two pints of urine are excreted in the twenty-four hours, the injections are first reduced from every two to every four hours. The patient should also be encouraged to drink as much water as he can to flush the system. If, in spite of these measures, the specific gravity of the blood remains above normal and the urinary flow is scanty, subcutaneous or even slow intravenous injections of a pint or so at a time are indicated, as illustrated by Cases 3, 4, 6–8 in Table VII, page 117.

Secondly, cardiac tonics should be given to increase the force of the heart. For this purpose

I generally inject subcutaneously one-hundredth of a grain of digitalin morning and evening, this drug being omitted from the ammonia mixture if that is being taken. If these measures are not successful, I next give one-hundredth of a grain of strophanthin intravenously not less than twelve hours after the last dose of digitalin and have several times found it to be effective in restoring the renal secretion. It is said to have the advantage of dilating the kidney vessels at the same time that it raises the general blood-pressure. Tabloids can readily be dissolved in a small quantity of water and injected by means of a small hypodermic syringe into one of the veins about the elbow, which have been made to stand out by a bandage applied above them. Care must be taken not to inject strophanthin into the subcutaneous tissues, as it is very irritating. By drawing up a drop of blood into the syringe before injecting, the fact of the vein having been entered is made certain.

Vaso-constrictors, such as adrenalin and pituitary extract, are also of great value in raising the blood-pressure to the desired height. The former may be given, both in the rectal salines and hypodermically, in 10- to 20-minim doses of the one-in-a-thousand solution every four to six hours. Intravenously, in very high dilutions, such as 1 in 100,000, it may also be of value in flushing the kidneys, but caution is necessary in this use of the drug on account of the danger of the sudden high pressure thus induced on the already enfeebled

heart, especially in elderly patients. The effects of adrenalin are also of short duration, although it will constrict the renal as well as the other vessels. For these reasons pituitary extract is of greater service, owing to the rise of pressure lasting longer, and I have several times found it of great service in threatened uræmia due to deficient blood-pressure after cholera.

Irritant diuretics, such as turpentine and cantharides, are most injurious, and should never be given.

Dry Cupping over both loins, not less than three cups being applied at a time, is also carried out twice daily until the kidneys act freely, as it helps to relieve the congestion of the organs. I have also tried wet cupping for actual uræmia, but cannot say I have seen any advantage from this more severe measure which in any way outweighs the inconveniences attending it.

Hot-Air Baths have been recommended in post-choleraic uræmia, and I have several times resorted to them, but have not seen much benefit result from their employment. They have the serious disadvantage of exhausting the patient and lowering the blood-pressure, and my results have been better since I employed them less. Should, however, the blood-pressure be above normal, which is rarely the case after cholera and the urine scanty without complete suppression, they may possibly prolong life, and thus give time for the action of other remedies.

In one case of continued suppression, with a blood-pressure of about 105 mm. in a woman, I got Major C. R. Stevens, I.M.S., to decapsulate and incise one kidney, but without succeeding in restoring its functions. Post-mortem early cirrhotic disease was found, which accounted for the failure of the operation. I have also punctured the kidney from the loin with an exploratory syringe and drawn off some blood with a view to relieving the intense congestion in uræmic cases, but I was not successful in saving any of the few desperate cases in which this measure was used. A stout needle of two and a half inches in length should be inserted just below the last rib and immediately outside the erector spinæ muscle, and made to pass obliquely inwards, forwards and a little upwards for its full length and suction is then applied. I have found the puncture marks post-mortem on the posterior surface of the organ about half an inch inside the convexity.

The inflammatory and gangrenous sequelæ, described on pages 124–6, must be treated on ordinary medical and surgical principles.

Convalescence. In the absence of complications and with careful regulation of the diet as already described (see p. 222), patients recover their strength with remarkable rapidity after cholera, except in the case of aged or previously feeble subjects. It is important not to allow any sudden exertion, such as sitting up in bed, for a few days, as the heart may be feeble for a time after the

stress of such an exhausting disease. Once, however, a fairly full diet can be safely given the convalescence is quick, and it is often possible to send the patient away for a change within ten days of the cessation of acute symptoms, while it is rarely necessary to invalid a patient to Europe if good health was enjoyed previously to the attack. The rapid restoration to vigorous health is one of the most satisfactory features in the treatment of cholera, which will be robbed of more than half its terrors for those who can be efficiently treated at a fairly early stage, if the results obtained by myself and others by means of the system of treatment described in the foregoing pages are confirmed by further experience.

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Oxford: Horace Hart, Printer to the University